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OF THE

RHEUMATIC DISEASES

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of the

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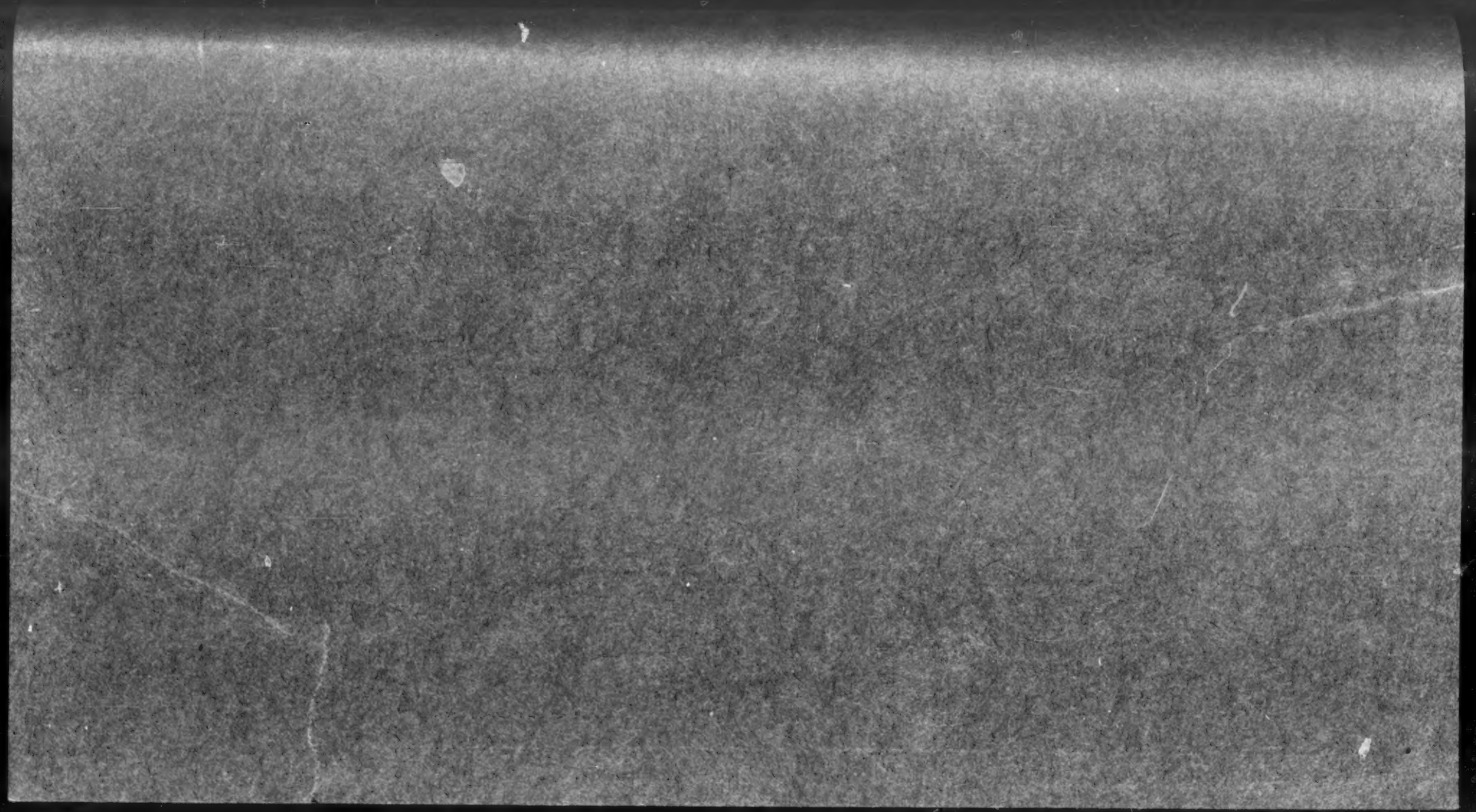

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ANNALS

OF THE

RHEUMATIC DISEASES

THE OFFICIAL JOURNAL OF

THE EMPIRE RHEUMATISM COUNCIL

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This Journal is the continuation of the "Reports on Chronic Rheumatic Diseases" hitherto published by authority of the British Committee on Chronic Rheumatic Diseases of the Royal College of Physicians. That Committee has transferred responsibility for the publication to the Scientific Advisory Committee of the Empire Rheumatism Council.

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PREFACE

In presenting the second number of The Rheumatic Diseases the Editors wish to express their appreciation of the valuable survey of American work and literature contributed by Dr. Philip Hench of the Mayo Clinic, which continues the similar reviews which have hitherto appeared in the " Annual Reports on Chronic Rheumatic Diseases." The survey represents an enormous amount of work on the part of Dr. Hench and his colleagues, and will be of the greatest interest and value to the British workers in the same field.

In this issue will also be found reviews of work done in foreign countries, and it is hoped to make this a feature of the journal. The Editors will be glad to receive reprints of any original work or research which might otherwise escape their notice.

It has been necessary to defer publication in this issue of some papers owing to pressure on our space. These will appear in the next number, which will be published in July. The fourth number will appear in October.

It is the aim of the Scientific Advisory Committee to make this journal the medium for the publication of new and original work on the Rheumatic Diseases which might not otherwise obtain the notice it deserves, and thus to make the journal indispensable to all who are interested in the campaign against rheumatism.

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THE RHEUMATIC DISEASES

THE ÆTIOLOGICAL PROBLEM OF RHEUMATISM

By WALTER LEVINTHAL

Our knowledge of the pathology of rheumatism has undergone a remarkable advance during the last quarter of a century owing to the discovery of three basic facts. The first is the definite recognition that the rheumatic damage is localised or at least originates in the *mesodermal* apparatus of the body. Whether rheumatism manifests itself as arthritis or fibrositis or neuritis, whether the skin or a bloodvessel or a visceral organ is the dominating site of the disease, it is always the connective tissue of the involved organ which is the point of attack. The second fact is the general character of the disease, even if in individual cases one single organ or limited area appears to the patient and to the clinician as the only affected part. Rheumatism is a *systemic* illness. The third fact concerns the rheumatic tissue damage itself in its *morphological* characteristics and development. The discovery of the Aschoff nodule (1904) was the starting point of this line of research. The specific rheumatic granuloma of mesodermal cells, however, represents only the second, subacute stage of the alteration. It is preceded by a hyperacute exudative stage, an œdematous swelling of the ground substance and the fibril bundles with central necrosis (Frank, 1912; Talalajeff, 1921; Klinge's " fibrinoides Frühinfiltrat "). The secondary immigration of cells into this early infiltration forms the granuloma with its central necrosis and surrounding inflammation, which may finally heal up by the proliferation of fibrous tissue and the formation of a minute rheumatic scar.

It is this feature of a characteristic mesenchymal structure with its developmental sequence, observed in all rheumatic conditions including gout, which has brought home to an ever-increasing number of investigators the idea that all forms of acute, secondary chronic, and primary chronic rheumatism belong to one nosological entity, the protean appearance of which is not

greater than that of tuberculosis. Final conclusions cannot, however, be drawn from pathological observation of tissues which only have at their disposal a limited range of response to a variety of irritants. A true nosological entity is based upon the evidence of a common causation. The final decision rests with the solution of the ætiological problem.

No enthusiasm for one or other ætiological claim can conceal the fact that the essential cause is still a matter of contention. The conception to be put forward in this article remains tentative. For the time being this conception seems to the writer the best working hypothesis able to explain all the available data.

It may be useful to review briefly some of the older theories. The discovery of deposits of uric acid led to the belief that gout is a disease due to the disorder of a metabolic function. Setting aside the mistake of interpreting the deposition of urates, which are an end product in man, as a metabolic disorder, it is now realised that the retention of uric acid is not the cause of gout, but a secondary phenomenon. On the analogy of gout, efforts have been made to attribute all rheumatic diseases to metabolic causes. These speculations are scarcely worth further consideration, although it must be borne in mind that factors of metabolic disorder might occur secondarily in the course of any systemic disease or could exert a precipitating effect on its development.

Recognition of the close relationship between the initial tonsillitis and rheumatic fever and the elucidation of the ætiology of the former infection initiated some fifty years ago the bacteriological era of rheumatology. A host of different bacteria, first amongst them the streptococci, have been held responsible for the disease, which thus was included in the group of infectious or infective diseases (Mantle, 1886; Achalme, 1891; Fraenkel, 1892; Netter, 1892; Poynton and Paine, 1900, and many others). This hypothesis regarded the rheumatic tissue damage as caused either directly by microbial invasion or indirectly by some bacterial toxin. Even for rheumatic fever, still less for the chronic rheumatic diseases, not much of the original idea has survived, stranded by failure to demonstrate with any regularity a definite germ at the site of the tissue change. The modified conception of an attenuated pyæmia (Sahli, Singer and others) was of no great avail, although it introduced an important new factor into the reasoning. In an attenuated infection there must be something that attenuates. The attenuating factor can only

come from the infected host. Consequently the outlook of these authors was more than before directed towards the reaction of the macro-organism.

The most modern variety of the old infection hypothesis is the suggestion that a virus is responsible. Be it admitted that this question is still *sub judice*, yet there seem to exist two arguments which speak rather eloquently against such a probability. The first is the difference between any virus-induced tissue lesion and the rheumatic granuloma. As Rivers, one of the most outstanding experts in the virus field, emphasises, every virus lesion shows as the primary change a hyperplastic cell reaction, usually followed by an exudative necrotic destruction. The basic pathological feature of primary fibrinoid degeneration in rheumatism, followed by invasion of cells and secondary formation of a granuloma, is inconsistent with everything known hitherto of any virus infection. The second objection concerns the strange selective affinity for the connective tissue which the supposed virus would have to possess. It is this specific localisation, the recognition of the mesenchyma as the point of attack, which should guide every ætiological research.

And yet, despite the ultimate failure of bacteriological research work in its efforts towards a final solution, there remains abundant evidence that infections are closely connected with classic rheumatic diseases, and that rheumatic symptoms may transitorily occur in the course of many, if not practically all, the classic infectious diseases. It was this knowledge which led Weintraud as early as 1913 to an entirely new conception, first applied to rheumatic fever and later extended by others to the whole group of rheumatism. The pith and pivot of this conception is the idea that the disease is not due to an external specific micro-organism, but to a *specific reaction of the macro-organism* to any invasion by a foreign protein, whether living or dead. The short paper by Weintraud states with remarkable lucidity nearly all the details which his successors have brought forward in favour of the idea that rheumatism is an *anaphylactic* condition. The much used and abused term of "allergy" will deliberately be banned from this article because of its ambiguity and vagueness. The useful paper by Freeman (1935) has discredited the word, but behind a word, even if wrongly or equivocally used, there sometimes lies a notion worth analysing. The essential point of the anaphylactic theory is the conception of the rheumatic syndrome as a

reaction of hypersensitive tissues to the agent which has specifically sensitised the cells.

Since Weintraud's pioneer article much pathological and experimental evidence has been brought forward to support the theory. Before 1913, quoted by Weintraud, Friedberger was the first to show that an aseptic arthritis can be produced by the intra-articular injection of horse serum in rabbits, provided the animals have previously been specifically sensitised. Klinge (1929) and Sonnenberg (1934) have demonstrated with the same technique the appearance of inflammation and degenerative tissue changes not only in the injected joint, but also in remote organs such as tendons, bloodvessels, muscles, the myocardium and the endocardium. A great stimulus has been provided by the work of Roessle and his school (from 1914 on), who studied the pathomorphology of the local tissue reaction in sensitised animals at various sites of " Erfolg " injection, and discovered the striking fact that the damage selectively concerns the mesodermal apparatus and produces a type of inflammation closely resembling the classical rheumatic granuloma with its three developmental stages. The histological investigation of the Arthus phenomenon by Gerlach (1923) is an example of this line of research. The new term of " hyperergic inflammation," invented by Roessle and adopted by other writers, does not seem to stand a logical analysis of the facts, as will be seen later.

While these earlier studies were confined to the examination of the anaphylactic reaction in directly inoculated tissues, more recent experiments, chiefly by Klinge and his numerous coworkers, have been focussed on the development of disseminated anaphylactic effects after intravenous injection of foreign substances in specifically sensitised animals. There is not room here to review in detail the important results. It is enough to state that the sequence of events is exactly the same following both modes of inoculation, with the self-evident difference that the attack from the general circulation produces anaphylactic reactions in many and sometimes in all parts of the hypersensitive mesenchyma. The second result of these investigations is the elucidation of the secondary factors which are able to direct the attack after intravenous injection to chosen areas, a problem to be discussed later.

To interpret all these investigations and experiments it is instructive to start with the point of view of Roessle, which has

been accepted by Klinge, Talalajeff, etc., and is summarised in the term "hyperergic inflammation." It is known that the first contact of a tissue with a harmless foreign substance, called antigen, releases only a slow local process of resorption, cleavage and digestion which has been pertinently called normergic. It is known that the contact of the same harmless substance with the same kind of tissue gives rise to a violent reaction, if the tissue has had previous experience with the particular antigen in question and has developed a greater ability to deal with it. It is generally accepted that this increased digestive capacity is due to the formation of specifically acting ferments or ferment-like functions, called antibodies, during the previous contacts. No objection could be raised against the name "hyperergic reaction" as long as the application of the term remains reserved for the increased function of digestion. But where does the essential element of inflammation arise? Roessle apparently regards the normergic reaction as a sort of micro-inflammation and looks upon the exudative degenerative process in the sensitised tissue as a mere enhancement of the normal physiological response. Klinge, following the same line of reasoning, admits almost unconsciously on several occasions that "in the normergic organism many antigens are resorbed *without or almost without any* tissue reaction"; he states that the antigen (foreign protein) does not act *at all* in the normergic organism or releases no signs of inflammation *whatsoever* (italics mine). No doubt the sensitised tissue responds with increased or hyperergic activity on the antigen, but this hyperactivity concerns only the digestion and elimination of the foreign substance. Can the increase of a normal metabolic function give rise to the intensive tissue damage that we call inflammation? An inflammation is the response to an irritation. The presence of an antigen in a tissue which is hyperergically equipped with the means for its elimination cannot be regarded as such an irritant. Briefly, the hyperergic metabolic function of the specifically trained tissue is an incontestable fact, but not the cause of the inflammatory reaction following with regularity the contact of the antigen with the tissue in a previously treated organism. It is not this inflammation which can reasonably be called hyperergic.

All these inconsistencies disappear at once if we follow the interpretation of the anaphylactic phenomena developed by the modern experts—*e.g.*, Dale, Doerr, Zinsser, etc. What happens

first and instantaneously, whenever and wherever an antigen meets with the corresponding antibody, is an interaction between these two substances, a combination and mutual fixation leading to a reaction similar to or identical with the well-known precipitation which we observe in our test tubes under such conditions. The older hypothesis (Friedberger) that this combined product of an innocuous antigen and an innocuous antibody represents a poison (anaphylactotoxin) has been abandoned. No toxic effect of such an antigen-antibody product *per se* can be demonstrated, unless the reaction takes place *inside* tissue cells. The modern science of anaphylaxis has universally accepted this *intracellular localisation* of the antigen-antibody clash as the salient point of the phenomenon. Not a toxic chemical product, but the purely physical effect of the intracellular reaction is the irritation which damages the cells.

The fundamental difference between the conceptions of Roessle and Doerr becomes at once evident. For Roessle it would be irrelevant whether the meeting of antigen and antibody and the succeeding intensified digestion occurs in the cells or in the tissue fluid around the cells; for Doerr it is only the intracellular reaction which irritates the cells and stimulates their inflammatory response. This is therefore the simple and shortest definition of tissue hypersensitiveness. Those tissue cells are hypersensitive to a given antigen, or potentially anaphylactic, which contain the corresponding antibody. The anaphylactic irritation becomes manifest if and whenever the antigen gains access to the sensitised (that is, antibody-equipped) cell. The inflammation which follows, the response to the physical cell irritation, is not hyperergic, but anaphylactic.

The name "anaphylactic," although clearly defined above, requires one more word of explanation from the historical angle. Originally the term was only applied to the dramatic phenomenon of shock produced by the intravenous injection of a sufficient amount of antigen in a specifically sensitised animal. This type of reaction, however, represents but the extreme example of a mechanism conditioned by exactly the same factors which govern any milder and more protracted form of hypersensitive reaction. The death of the anaphylactic guinea-pig is due to the sudden extensive and intensive irritation of the mesenchyma in the bronchioli, but in fact the reaction occurs in all parts of the sensitised organism—*e.g.*, in the uterus and the intestines as

demonstrable by the experimental arrangement of the Dale or Massini technique, or in the liver. This irritation of the liver mesenchyma is quite harmless for the guinea-pig, but is responsible for the anaphylactic collapse and death of the dog. In fact, the anaphylactic irritation occurs in the whole of the sensitised mesenchyma, but the fatal issue is only related to that small sector of the general reaction which concerns the so-called shock organ, different in different animal species. The rarely fatal anaphylactic shock of man gives evidence of the participation of many, if not all organs (cardiovascular apparatus, lungs, intestines, central nervous system, etc.). The vehemence of these anaphylactic shocks is only caused by the suddenness and intensity of the effect if the antigen inundates the whole organism. No immediate and dramatic effect is produced by the same antigen if only minute amounts reach the sensitised tissues, but the inflammation following a repeated or continuous influx indicates the successive irritation which could be properly called anaphylactic micro-shock.

The quantity in space (amount) and time (once, repeatedly, continuously) is an essential factor governing the type and the clinical and pathological consequences of an anaphylactic reaction. It is equally obvious that the point of access has a decisive influence in determining the localisation of the anaphylactic damage. The sensitisation of a hay-fever patient is not confined to the subepithelial mesodermal skeleton of the respiratory mucous membranes (proof: skin test), but it is only here that the pollen antigen from outside comes into contact with the hypersensitive tissues. It will be seen later that a circulating antigen, too, can be restricted to special points of access, to a single part of the sensitised system, by the influence of non-specific secondary factors. The reader's imagination is invited to visualise all the possibilities of type, intensity and localisation of changes which are essentially of the same nature—namely, consequences of an anaphylactic cell irritation.

Hypersensitiveness depends upon cell-fixed antibodies. These antibodies are the result of previous contacts with the antigen which has stimulated the mesodermal system to the specific response. The next step in this argument is therefore the definite conclusion that every kind of contact with an antigen must lead to sensitisation of the antibody producing tissue cells. The great bulk of such contacts consists of microbial

invasions, whether saprophytic or pathogenic. Indeed, this theoretical conclusion is borne out by the facts. In the course of every infectious disease there arises a specific tissue hypersensitiveness demonstrable, for instance, by skin tests. It starts soon after the infection; in acute diseases it outlasts the presence of the infecting germ for a considerable but variable period, and disappears by the gradual elimination of the antibodies which are no longer reproduced in the absence of the antigen; it persists permanently, if the antigen persists, as in chronic infections. It is important to emphasise that this hypersensitiveness is strictly confined to those tissues which are concerned with the function of antibody production. Hypersensitiveness is a unique feature of the mesenchyma.

Does such a mesenchymal sensitisation constitute a condition of *general* hypersensitiveness ? The answer is simple and clear: obviously only if a second condition is fulfilled. The intracellular antigen-antibody reaction is only possible if the antigen reaches the antibody containing cells. Artificially this access can be forced by a direct local inoculation. Under natural conditions, however, the antigen has no avenue to most tissues except by way of the circulation. This might appear to be easy of achievement, but in fact it is not. All the routes leading from the site of infection, where the microbes have settled, where they live, multiply, die and pour out their dissolved body substance (the antigen) into the surrounding tissue fluids—all these routes from the antigen source to the mesodermal tissue cells (the blood stream, the lymph spaces, the tissue fluid) do not allow free passage for the antigen. What does hamper and check the antigen and prevent its straight access to the cells and the cell-fixed antibodies? Let us look at a typical case of typhoid fever, or watch an experimental rabbit subjected to a course of injections with horse serum. The specific antibody (antityphoid here, antihorse there) is gradually produced in the cells of the mesodermal system, but very soon is also to be found freely circulating in the body fluids —*e.g.*, in the blood stream. The production centres do not retain the whole amount of their output to store it as cell-fixed antibody (Ehrlich's sessile receptor), but cast off a portion of it and pour it out into the circulation (Ehrlich's free receptor). Now imagine the sequence of events in a system equipped with fixed *and* freely circulating antibody, when the antigen enters the body fluids and starts its journey to the tissues. All the way along it meets

with the antibody, combines with it, is fixed and arrested *within the circulation*, so that not a trace of unchecked antigen escapes and reaches the cell-stored antibody.

This, indeed, is the second condition for the establishment of general hypersensitiveness: the absence of free antibody in the circulation. " Absence," of course, is an exaggeration, describing the extreme case of a quasi 100 per cent. condition of anaphylaxis. The quantitative factor is decisive. Whenever the amount of free antibody is insufficient to neutralise the total amount of circulating antigen, that portion which escapes and makes contact with the antibody in the cells gives rise to an anaphylactic tissue reaction.

It is advisable to introduce here the term for the fully developed state of antibody equipment in all parts of the system—immunity. Originally derived from the clinical observation of specific resistance against the infective or toxic aggression of a germ, the term is equally applicable and, indeed, applied to every form of specific counteraction against a foreign substance by means of antibodies. We " immunise " a rabbit against horse serum. Sensitisation is a legitimate part and stage in every immunisation. The hypersensitiveness of the mesenchyma is an inseparable feature of immunity, but the general hypersensitiveness or the *anaphylactic condition* is characterised by a *particular distribution of the antibodies with a preponderance in the mesodermal cells and a deficiency in the circulation.*

The conception of rheumatism as an anaphylactic condition was based on clinical intuition (Weintraud) and pathological and experimental observation (Roessle, Talalajeff, Klinge), showing the correspondence between the rheumatic and the anaphylactic lesion in localisation, development, and histomorphology. The basic *serological* feature of anaphylaxis, the characteristic distribution of antibodies, has but rarely and in an indirect way attracted the attention of rheumatologists. Out of a vast sea of serological studies on rheumatism following the familiar track of investigations on infectious diseases, as a legacy from the bacteriological era of rheumatology, only a limited number of publications relate to the anaphylactic problem. Prominent among them are the experimental studies of Swift and his co-workers on the distribution of antibodies after different modes of immunisation and Coburn's illuminating observations on rheumatic fever. The sole direct evidence of this anaphylactic

antibody distribution in rheumatic patients appears to have been contributed by my results from comparative precipitation and agglutination tests of serum and joint fluid in cases of chronic rheumatism (Levinthal, 1938).

That a joint fluid is a suitable material for serological examination was shown by Nicholls and Stainsby (1931) in three cases of rheumatoid arthritis with a " surprisingly high " titre of streptococcal agglutinins, but no comparative study was attempted and no conclusion was drawn from the demonstration of the intra-articular antibody in this small series. Simultaneous tests of serum and joint fluid for agglutinins against streptococci were reported by Blair and Hallman (1935). A table summarising the results of five cases of rheumatoid arthritis, three cases of gonorrhœal arthritis, three cases of osteo-arthritis, and nine controls contains in the first group one case with a serum titre of 640 and a joint-fluid titre of 5,120, but no attention is called to this striking contrast.

My serological investigations, carried out at the Royal National Hospital for Rheumatic Diseases in Bath from 1936 on, were based on agglutination and precipitation tests with a strain of *Streptococcus hæmolyticus*, group A, type 3, isolated from the throat of a rheumatoid arthritis patient, and sometimes in addition with the mucous variety of a *Streptococcus hæmolyticus*, group A, type 13, isolated from the sore throat of a non-rheumatic individual.

The technique of the agglutination tests followed the usual lines; 0·5 c.c. of an eighteen to twenty-four hours broth culture was mixed in ⅜-inch tubes with an equal amount of serum or joint fluid in falling dilutions and kept for two hours in a water bath of 56° C. with only one half or a little less of the fluid column submerged. The first reading, after slight shaking, was checked the next morning, the tubes having been kept overnight in the ice chest. Only the clear-cut formation of conglomerates was counted, a mere sedimentation, even if very marked in comparison with the homogeneous suspension in an always included negative control serum, being considered as negative. The broth used was the plain medium, prepared from tryptically digested veal meat by extraction at pH 6·9 to 7·1, containing the whole range of proteins from heat-stable but acid-coagulable albumen to the amino-acids (Levinthal, 1931, simplified since).

The same medium was used for the preparation of a very simple precipitation antigen. An abundantly grown twenty-four hours culture was spun, the almost clear supernatant fluid adjusted to pH 7·4 with *N* NaOH and filtered through a small Berkefeld V candle. A corresponding preparation from a strain of yeast (*Saccharomyces cerevisiæ*) was used as a control. Besides the broth filtrate antigen, representing all the microbial body substances which go into natural solution during growth, a crude C sub-

stance (group A specific carbohydrate) was often employed, prepared from the same streptococci strains in the following way:

The washed sediment of a young broth culture (six to eighteen hours) and/or the growth of a twenty-four hours culture on blood agar (the agar being the same "albuminate tryptone" medium as the broth) were dissolved in a slightly warmed 10 to 15 per cent. aqueous solution of alkaline hypochlorite (antiformin substitute B.D.H.), the smallest total amount necessary for the complete solution of the cocci being used. The clear fluid was boiled up and acidified with *N* HCl until the maximal precipitation of the protein was obtained. After standing overnight at room temperature and centrifuging, the clear supernatant fluid, which should be completely negative to the most rigorous sulphosalicyl test (saturated solution, first ring test, then mixed), was mixed with 30 volumes of acetone. After some hours the copious flocculent precipitate was collected by centrifuging, washed with acetone, dried and redissolved in the smallest necessary amount of distilled water. The readily dissolved substance, after discarding the trace of insoluble sediment, was precipitated with acetone and treated in the same way as before for a second time. The white powder was dried and stored in an exsiccator. A standard solution of this C antigen, $_{2}\delta\delta$ or $_{2}\delta\delta$ in a phosphate buffer pH 7·4, was diluted for the tests with saline to $_{1}\delta^{1}\delta\delta$, $_{2}\delta^{1}\delta\delta$ or more.

All the precipitation tests were done in ¼-inch tubes with 0·2 c.c. of antigen and 0·1 c.c. of undiluted serum or joint fluid. Any alteration of this quantitative relationship, as increase or decrease of either the broth antigen (from 0·5 to 0·1 c.c.) or the serum (or fluid) (from 0·2 to 0·01 c.c.), carried out repeatedly in order to counter the possible objection that the condition of optimal proportions (Dean and Webb) had not been taken into account, has never changed the original result.

It goes without saying that serum and joint fluid have to be as clear as possible. Blood was withdrawn from the patient three and a half to four hours after breakfast, which gave almost invariably a serum free of chylous turbidity. The clarification of a joint fluid is more difficult. The aspirated fluid was kept in a large test tube for some hours or overnight at room temperature and spun after any coagulum had been broken up by shaking or whipping with a platinum wire. This procedure had to be repeated the next day, because even a perfect clarity after the first centrifugation proved too often to be fallacious. Although I always succeeded even with exudations of rather high viscosity in obtaining by this simple method a perfectly suitable fluid on the second day, I should like to quote the personal suggestion of Dr. Douglas H. Collins (Harrogate) to use a sand and paper pulp filter for the final clarification of a particularly obstinate joint fluid.

The serum or fluid was run along the glass wall into the antigen to form a separate layer at the bottom of the tube. At the first reading after twenty to thirty minutes in the incubator the formation and eventually the intensity of a ring was noted, serving as an inconclusive forecast for the final result. The tubes were kept overnight at 37° C. The amount and type of the precipitate was noted by the number of crosses, the sign ××××× indicating the formation of a compact disc, as characteristic of the precipitation of a carbohydrate. After this reading the tubes were spun for half a minute and the result checked macro- and microscopically. The

precipitates with the C substance consisted always of transparent confluent yeast-like droplets, the sizes of which corresponded with the intensity of the reaction. The broth antigen usually gave compact floccules composed of small granular particles or minute droplets. A loose friable flocculation, consisting of a fine network of filaments, characterises a protein precipitation (noted by the ordinary cross, +), as seen in the serum of some rabbits treated with infected subcutaneous agar clots, if tested with the broth antigen or pure broth as control.

It may be permitted to reproduce here Table III. from the above-mentioned publication, summarising a comparative study of serum and joint fluid from forty-four patients, thirty-nine of them representing the Group II. of rheumatoid arthritis (thirty-five) and acute infective arthritis (four), and the other five Group I., with a diagnosis other than rheumatoid arthritis—namely, two gout, two spondylitis, one doubtful rheumatoid on an old osteo-arthritis.

SERA AND JOINT FLUIDS COMPARED.

	No.	*Fluid Positive, Serum Negative.*	*Fluid Stronger than Serum.*	*Both Equal.*	*Fluid Negative.*
I.	5	0	0	0	5=100·0 %
II.	39	8=20·5 %	12=30·8 %	16=41·0 %	3=7·7 %

The results demonstrate the extreme case of an exclusive presence of the streptococcal antibodies in the joint fluid in 20·5 per cent. and their preponderance in the fluid over the serum in 30·8 per cent. more cases of Group II. The following interpretation was given:

"A synovial fluid being of dual origin, one part being derived locally from the intra-articular tissues, the other merely a serum- or lymph-derived transudate, it is obvious that substances demonstrable in a joint fluid while absent in the serum must come from the diseased and broken-up joint tissue itself. The serological results therefore point to a particular distribution of antibodies, to their presence in tissue cells and their absence or lesser amount in the circulation."

This direct evidence of an antibody distribution characteristic of the anaphylactic condition could be confirmed by skin tests with the same antigens. The significance, however, of skin tests

with an antigen of such almost ubiquitous occurrence as streptococci remains restricted. A positive result proves nothing more than a previous contact with the antigen, and is common to the sensitised and the immunised individual.

The scrutiny of the table suggests one more conclusion. It is seen that almost 8 per cent. of cases in the rheumatoid group show no serological relationship at all to the streptococci. On the other hand, in a series of tests with serum alone from 266 patients, comprising all groups of chronic rheumatism, a relation to streptococcal infections was also revealed in approximately 25 per cent. of cases of osteo-arthritis, fibrositis and spondylitis (as compared with 71·8 per cent. in the rheumatoid group, if only the serum results are considered). It is therefore evident that the results do not warrant the conclusion that streptococci are specifically connected with rheumatoid arthritis. In a number of cases in this group and in the majority of cases of fibrositis, spondylitis, etc., which are only topographically different from rheumatoid, but possess the same mesodermal localisation and histomorphology, other germs of chronic infection may be held responsible for the initial invasion which has developed into the consequent rheumatism. No particular microbe can be regarded as the specific causative agent of any rheumatic condition. Even a variety of antigenic factors may simultaneously and identically act in one and the same individual.

It becomes clear, moreover, that the state of hypersensitiveness is not confined to invasions by a living micro-organism. The antigenic effect of any foreign substance on an individual with the described type of response would be bound to produce a rheumatic or similar condition if the antigen were to attack the mesenchyma from the circulation. The insidious and slowly progressing development of a chronic rheumatic process points to the persisting influx of an endogenous antigen, originating from the site of chronic infection, either focal or superficial on respiratory and intestinal or other mucous membranes. The explosive onset of classical gout is more consistent with the assumption of an exogenous antigen which only enters the circulation occasionally —*e.g.*, an element of the food. The connection of gout with alimentary factors, always suggested by clinical experience, includes, of course, the supposition that antigenically acting substances from the food are absorbed through a breach in

the intestinal epithelium before their complete cleavage and denaturation.

Gout, released by the *systemic* invasion of an *exogenous* antigen, appears in this conception as a link between the anaphylactic "attack diseases" (Aschoff) like hay fever and asthma, released by the *local* contact of an *exogenous* antigen with sensitised surface structures, and the insidious forms of rheumatism, released by the *systemic* attack of an *endogenous* antigen. They all have in common the specific factor of a sensitised host, deprived of the protective barrier of freely circulating antibodies to prevent the detrimental intracellular antigen-antibody reaction and consequent anaphylactic inflammation of mesodermal tissues.

There is not room here for more than a condensed reference to the important and most illuminating studies concerning the problem of the *organ localisation*. What is the reason for the elective localisation of the tissue damage when all parts of the organism are liable to attack by a circulating, evenly distributed antigen? The very striking Auer phenomenon was the clue and starting point for numerous experiments by Klinge and his co-workers (summed up by Roessle, 1936, and Klinge, 1937). It is possible to localise at will an anaphylactic tissue reaction after intravenous antigen injection and to concentrate it in a predetermined area. The so-called Auer phenomenon is as follows: In a sensitised rabbit no visible reaction occurs after intravenous injection of a small amount of antigen; but if during the period when the antigen circulates one skin area—*e.g.*, one ear—is temporarily congested by xylol, a violent anaphylactic inflammation or Arthus phenomenon results after some time at the spot of the transient artificial hyperæmia. The application of a great variety of thermic, traumatic and pharmacological stimuli enables the experimenter to direct the brunt of the attack by the circulating antigen to a selected part of the sensitised mesenchyma. The explanation is obvious. The common factor of all these operations is the production of a temporary hyperæmia with dilated capillaries, stasis, retarded rate of blood flow, and an increased permeability of the endothelial lining of the blood-vessels. Transient as this reaction may be, it suffices to accumulate the circulating antigen in a circumscribed area and to open here the endothelial barrier, so that the concentrated antigen diffuses into the surrounding tissue. Roessle has proposed the

term " epigogy " for the phenomenon (ἐπάγειν, to guide down, to conduct).

It must be remembered that the very same phenomenon has been well known for many years (without the new word) from wide clinical and experimental observation of generalised infections, dating back to an experiment by Calmette and Guérin in 1901. The whole history of the relationship between local tissue injury and the localisation of generalised infections has been reviewed and enriched with new data by Findlay (1928), who suggests that the liberation of histamine by the injured tissue is the essential denominator of all the various chemical, thermal or mechanical stimuli which cause " (1) the primary and local dilatation of the capillaries, (2) a widespread dilatation of the neighbouring strong arterioles brought about through a local nervous reflex, and (3) locally, increased permeability of the vessel walls."

However, it must be borne in mind that these adjuvant irritants direct only the conspicuous brunt of the attack; as emphasised in the introduction, no isolated localisation tells the whole story of a rheumatic disease, and the experienced clinician as well as the pathologist will also detect the minor symptoms of the systemic dissemination.

The anaphylactic theory of rheumatism appears to supply the best explanation for all the protean traits of the disease and its conditioning factors, but is it much more than the substitution of one riddle by another ? Why is it that one individual becomes immunised under the antigenic impact of a foreign substance, while another is sensitised, the antibodies being exclusively or mainly located in the cells ? Only a convincing answer to this question would offer a real solution of the ætiological problem of rheumatism. An approach to this problem from a simple quantitative angle suggests a solution.

Immunisation and sensitisation are phenomena not qualitatively, but only quantitatively different, sensitisation representing a state of *imperfect* immunisation. Three chief groups of individuals may be distinguished, differing in their quantitative capacity of response to any immunising stimulus:

Group I. is characterised by a more or less complete debility of the antibody producing system which might be called *anergic*. This debility can be constitutional or temporary, under the influence of paralysing factors such as intoxications. Individuals

of this type perish as helpless victims of general sepsis following infections.

Group III. (at the other extreme) is the ideally normal vigorous type with fully developed capacity for antibody production. The prompt and abundant response not only checks at once the spread of an infection, but equips the whole organism with a surplus of antibodies, overflowing from the centres of their production into the circulation, sufficient to deal with and to dispose of any amount of persisting antigen. A *perfect* immunisation is the result of this full capacity of defence which could be called *panergic*.

In Group II. the response is of an intermediate order. The patient neither completely fails to react nor is able to proceed to the state of perfect immunity. Individuals of this type, too, become finally immunised as far as the specific protection of the tissues is concerned, but the antibodies, more sluggishly and less amply produced, remain chiefly confined to the tissue cells without a surplus for the circulation. It must be stressed that even such an *imperfect* immunisation is quite sufficient to overcome the specific infectious disease. A typhoid fever ceases to be typhoid fever, a streptococcal infection is no longer the specific infectious disease. An entirely new pathological reaction, no longer typhoid or streptococcal, or whatever the case may be, has been conditioned—namely, the state of anaphylaxis by virtue of the same antibodies which have caused the recovery from the original disease. They have established the hypersensitiveness of the mesenchyma to the antigen, which gains access to the tissue because unchecked by freely circulating antibodies. These " second diseases " are essentially identical whichever infective germ or other antigen may have initiated the original immunising impact. The partial deficiency of the antibody producing system which is the basic factor responsible for this imperfect immunisation is neither anergic nor panergic, but could pertinently be called *hypoergic*. It seems a paradoxical result of this analysis that the term hypoergic offers itself for the condition which leads to the anaphylactic diathesis, contradicting the illogical concept of " hyperergic inflammation."

Obviously this hypoergic state of the mesodermal apparatus also can be of a constitutional or of a temporarily acquired nature, influenced by secondary factors such as malnutrition, climate, strain, endocrine disorders, physical and mental trauma or housing

conditions. All such precipitating factors do not directly act upon the disease, but indirectly by way of their debilitating effect which weakens the antibody producing system and incapacitates the carrier of a chronic antigen depot from proceeding to the state of perfect immunity.

I have tried in a limited number of patients to demonstrate directly this essential slowness and incompleteness of the antibody response. A preliminary skin test with the *yeast* antigen, mentioned above, proved by its frankly negative result the absence of any yeast antibody at the beginning of the experiment. A course of subcutaneous injections with a yeast vaccine twice per week was performed, and the time was determined at which (1) the skin test became positive, and (2) the precipitating antibody appeared in the serum. The result on one patient may be reported in comparison with a rabbit subcutaneously injected with the same vaccine. C. T. A. was a twenty-year-old man with an intensive rheumatoid arthritis of long standing refractory to all forms of treatment for a considerable time. Whereas his skin test became positive after the third injection, the first trace of a serum precipitation ($\mp$) was only obtainable after eighteen injections two months nine days from the start of the vaccination. It increased a month later after a total of twenty-four injections to a weakly positive result ($\times$). The rabbit, on the other hand, showed a strong precipitin response ($\times\times\times$) after the first four injections. It is proposed to pursue this promising scheme of investigation on a bigger scale, including all types of chronic rheumatism.

A last question arises concerning the contrast between the course of acute rheumatic fever and the insidious and progressive development of rheumatoid arthritis. In his serological studies of rheumatic fever Coburn comes to the conclusion: "In the rheumatic subject the development of the antibody response appears to be delayed." A similar conclusion was arrived at for rheumatoid arthritis in my paper before the Bath Congress. And yet, how different appears the clinical aspect of the two diseases from the onset to the end, apart from the dissimilarities in the topographical involvement. To say that one disease is the type of rheumatism in the juvenile organism, while the other is characteristic for the adult, is no explanation and, moreover, not quite consistent with the facts. Rheumatoid arthritis has been observed, although rarely, in children; rheumatic fever may

occur, although not often, at an advanced age. Still, the age factor remains a conspicuous element and gives the clue for the following interpretation. The *first* contact of an individual with an antigen raises the antibody curve from zero to increasing values. The period of the fateful antibody distribution associated with the rheumatic reaction is, as it were, reached from below. The average adult, on the other hand, has lived for years with many parasites in a well-balanced and undisturbed symbiosis by dint of a more or less perfect immunisation, until at a later period his weakened mesenchyma gradually loses the capacity to *reproduce* the necessary amount of antibodies and to keep abreast with the output from his antigen depots. Here the phase of the fateful antibody distribution is reached by a slow decrease of the serum antibody curve—that is to say, quasi from above. This interpretation is strongly supported by the fact that all rheumatic symptoms in the course of acute infectious diseases, supplying a fresh antigen, imitate the type of rheumatic fever and never of chronic rheumatism.

A glimpse may be thrown upon therapeutic experiences and possibilities in the light of the anaphylactic conception. It is evident that the natural or artificial elimination of the responsible antigen from the body interrupts with one stroke any rheumatic reaction. The transience of rheumatic symptoms in the course of acute infectious diseases is therefore partly explicable by the final disappearance of the antigen, partly by the fact that the anaphylactic state in these diseases is an intermediate phase in the process of immunisation before the appearance of the antibodies in the blood stream. In chronic infections the artificial removal of a septic focus (tonsils, teeth, inflamed gall-bladder) can only lead to the desired result if the removed organ contains the sole or at least the predominant source of the antigen, certainly a rare event. Even a full first success would be no guarantee against the recurrence of the disease at the very next occasion of a fresh infection.

The effect of gold, sulphur, protein shock, spa treatment, specific and non-specific vaccination rests with their stimulating influence upon the antibody producing system. Such influence is limited by the degree of reactivity left in the individual patient. Salicylates and calcium suppress temporarily the anaphylactic cell reaction, just as a general anæsthesia suppresses the anaphylactic shock.

A real cure of the rheumatic diathesis could only be expected

if a restitution of the antibody producing system were obtainable or a substitute therapy after the model of insulin were discovered, making up for the loss of a possible hormonal factor involved in the physiological function of antibody production.

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RESEARCHES INTO THE ÆTIOLOGY OF ACUTE RHEUMATISM

I.—RHEUMATIC CARDITIS: POST-MORTEM INVESTIGATION OF NINE CONSECUTIVE CASES

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By C. A. GREEN

Introduction

Westphal, Wassermann and Malkoff (1899) isolated streptococci from the blood, brain and heart valves of a girl dead as a result of acute endocarditis, and thereby initiated countless attempts to define the exact relationship between streptococcal infection and rheumatism. Independently and almost simultaneously Poynton and Paine (1900) recorded their first observations, in which they came to the conclusion that streptococcal infection was a cause of acute rheumatism. Among those workers who have reported confirmation of these findings may be mentioned Walker and Ryffel (1903), Beattie and Yates (1912), Lyall (1912), Swift and Kinsella (1917), and Clawson (1925). Probably an even greater number of investigators have recorded complete failure to recover organisms from any site in rheumatic subjects. Even in the successful series streptococci were recovered from the blood during life or after death, and only occasionally from the joint or cardiac lesions. These facts have given rise to the general conclusion that the cultural findings did not support the simple explanation that rheumatism was the result of the direct invasion of the joint and cardiac tissues by streptococci, but did not exclude the possibility that some association of more complex nature existed. Agonal and post-mortem bacterial invasion of the blood stream is of frequent occurrence, as shown by Wright (1925), and must be carefully considered in relation to post-mortem cultural investigations. There was no uniformity as regards the type of streptococcus isolated by successful investigators, and this again has thrown doubt on the exact significance of their findings. In most instances, however, the organism has been

of the alpha-hæmolytic variety, or, according to Birkhaug (1927), Small (1927) and Kriedler (1928), the organisms may be indifferent in type. At the present time death in the acute or subacute phase of rheumatic infection is uncommon, but the series of nine consecutive cases described below were observed in Edinburgh during the space of twelve months.

Methods

Collection of Specimens.—The bacteriological investigations were made during the course of the routine post-mortem examination, the shortest interval between death and autopsy being fifteen hours and the longest thirty-six hours. After opening the thorax any free fluid present in the pleural sacs was collected by means of a sterile syringe. The anterior surface of the pericardium was then seared while the heart was still *in situ*, and any free fluid in the pericardial sac was collected by means of a syringe plunged through the seared surface. The parietal pericardium was then partially reflected aseptically, and one or more pieces of any exudate present on both parietal and visceral surfaces were taken. The surface of the heart was then seared, and from 2 to 5 c.c. of heart blood were taken for culture, distributed as 1 c.c. volumes in 10 c.c. digest broth. The heart was then removed from the body, opened aseptically, and portions of any valves showing recent vegetations were cut into two or more fragments, each of which was cultured separately. No attempt was made to wash the valves free of traces of adherent blood. For controls, portions of valves without vegetations were taken from the same hearts.

Culture Media.—Horse digest broth: The medium described by O'Meara (1934) was used throughout in the primary culture of all specimens. In the case of fluids—*e.g.*, pericardial fluid—1 c.c. of the specimen was added to 10 c.c. digest broth. Tissue specimens were cut into small fragments, and each cultured in a separate tube of broth.

Blood agar plates: After twenty-four hours' incubation at 37° C. the digest broth cultures were plated on 5 per cent. horse-blood agar and incubated aerobically.

Serological Typing.—The slide agglutination technique described by Griffiths (1934) was used in the identification of strains of hæmolytic streptococci isolated by the above methods.

Results.

Nine consecutive cases of primary or recurrent rheumatic carditis were examined by the above methods, and twenty-two non-rheumatic subjects were similarly treated as controls.

Rheumatic Series:

Case 1.—C. C., female, aged fifty-three years.

Clinical Diagnosis.—Acute rheumatic endocarditis.

Clinical Features.—Admitted to hospital in fourth attack of acute rheumatism with obvious signs of established endocarditis. She developed acute congestive failure after the subsidence of joint pains. Hæmolytic streptococci, type 27, were isolated from the throat ten days before death.

Post-mortem Findings.—The pericardial sac was completely obliterated by fibrinous adhesions, no free fluid being present. The heart showed generalised dilatation, with marked hypertrophy of the left ventricle and auricle.

Tricuspid valve: Areas of old fibrous thickening, and several small, recent vegetations of rheumatic type.

Mitral valve: Gross stenosis due to old fibrous thickening of chordæ tendineæ, with several recent vegetations on auricular surface.

Aortic valve: Fibrous lesions, resulting in partial adhesion of cusps, but no evidence of recent endocarditis.

Pulmonary valve: Healthy.

There were no vegetations of the ulcerative type nor those associated with subacute bacterial endocardial endocarditis. The lungs, liver and spleen presented the appearances produced by venous congestion, and no infarcts were detected.

Cultural Results:

Heart blood	Tube 1. *B. coli.* Tube 2. *B. coli.*
Tricuspid valve ..	Tube 1. Hæmolytic streptococci, type 27, and *B. coli.* Tube 2. *B. coli.* Tube 3. No growth.
Mitral valve	Tube 1. Hæmolytic streptococci, type 27. Tube 2. Hæmolytic streptococci, type 27, and *B. coli.* Tube 3. *B. coli.*
Aortic valve	Tubes 1, 2 and 3. No growth.
Pulmonary valve ..	Tube 1. *B. coli.* Tube 2. No growth.
Pericardial exudate ..	Tube 1. Hæmolytic streptococci, type 27. Tube 2. Hæmolytic streptococci, type 27.

Microscopic Examination.—Sections of mitral valve, stained by hæmatoxylin and eosin, showed fibrous scarring with persistent vascularisation. There was superficial necrosis and new formation of vegetations, but little or no cellular reaction. Sections of myocardium showed a few small areas of fibrosis, but no Aschoff bodies. Sections of mitral valve and myocardium, stained Gram, showed no organisms.

Case 2.—G. B., male, aged twenty-two years.

Clinical Diagnosis.—Rheumatic carditis, mitral stenosis and incompetence.

Clinical Features.—Rheumatic fever had occurred at the age of eight years. Two years before present attack patient had been treated for auricular fibrillation. He was admitted to hospital with mitral stenosis and incompetence, and, on improvement, was transferred to a convalescent home. He continued to progress favourably until he "caught a cold," and had then to be readmitted to hospital. At this time a throat swab yielded a heavy growth of hæmolytic streptococci, type 14. He then developed the typical rheumatic syndrome with severe pains in both wrists, ankles, and knees. Pericarditis supervened, and the additional stress on an already failing heart ended in death.

Post-mortem Findings.—The peritoneal cavity contained more than a pint of clear serous fluid. The pericardial sac was grossly distended, containing a quart of fluid. Both parietal and visceral layers of the pericardium were covered with fresh fibrinous exudate. Posteriorly the sac was obliterated by adhesions between the two layers. All chambers of the heart were dilated, particularly the left auricle and ventricle.

Tricuspid valve: Apparently healthy.

Mitral valve: Both cusps slightly thickened, and the chordæ greatly shortened. There was a complete line of vegetations along the margin of the valve.

Pulmonary valve: One small area of fibrosis.

Aortic valve: Old-standing fibrosis, but no recent lesions.

Cultural Results:

Heart blood	.. ..	Tube 1. No growth. Tube 2. No growth.
Pericardial fluid	..	Tube 1. No growth. Tube 2. No growth.
Pericardial exudate	..	Tube 1. Hæmolytic streptococci, type 14. Tube 2. Hæmolytic streptococci, type 14.
Tricuspid valve	..	Tube 1. No growth. Tube 2. No growth.
Mitral valve	.. ..	Tube 1. Hæmolytic streptococci, type 14, and *B. coli.* Tube 2. *B. coli.*
Aortic valve	.. ..	Tube 1. *B. coli.* Tube 2. No growth.

Case 3.—D. F., female, aged thirty-three years.

Clinical Diagnosis.—Acute rheumatic fever.

Clinical Features.—Ten days after recovering from an attack of tonsillitis, which lasted one week, acute polyarthritis of the limbs appeared. This continued for five weeks, when acute endocarditis was manifest. After admission to hospital hæmolytic streptococci, type 18, were isolated from the throat. The patient became increasingly breathless, and died after a period of respiratory distress.

Post-mortem Findings.—The pericardial sac contained about 2 c.c. of fluid, but the two layers of the pericardium were gummed together by fresh fibrinous exudate, and tore apart to leave the shaggy surfaces typical of an acute rheumatic pericarditis. The pleural sacs contained considerable quantities of serous effusion.

Tricuspid valve: No macroscopic lesions.

Mitral valve: Typical minute vegetations along the line of closure, and a slight degree of older thickening of the posterior cusp.

Aortic valve: Complete ring of minute fresh vegetations.

Pulmonary valve: No macroscopic lesions.

The right upper lobe of the lung showed a patch of confluent bronchopneumonia which was apparently terminal.

Cultural Results :

Heart blood	Tubes 1 and 2. *B. coli.* Tube 3. No growth.
Mitral valve	Tube 1. Hæmolytic streptococci, type 18, and *B. coli.* Tube 2. Hæmolytic streptococci, type 18, and *B. coli.*
Aortic valve	Tube 1. Hæmolytic streptococci, type 18, and *B. coli.* Tube 2. Hæmolytic streptococci, type 18, and *B. coli.*
Pulmonary valve ..	Tube 1. *B. coli.* Tube 2. *B. coli.*
Pericardial exudate ..	Tube 1. Hæmolytic streptococci, type 18. Tube 2. Hæmolytic streptococci, type 18.
Pericardial fluid ..	Tubes 1 and 2. No growth.

Case 4.—E. S., female, aged fourteen years.

Clinical Diagnosis.—Rheumatic endocarditis, terminal ? meningitis.

Clinical Features.—This girl had acute rheumatism at the ages eleven and thirteen years. After the second attack mitral stenosis and incompetence appeared. In a convalescent home patient continued to have frequent pains in her legs and arms. Septic tonsils were removed, but the increasing dyspnœa and œdema of the legs resulted in readmission to hospital. On the second night she complained of headaches, and there was slight neck rigidity. She died at 10.30 a.m. the following morning.

Post-mortem Findings.—The pericardial sac contained 2 c.c. fluid, and in the abdominal cavity was a considerable volume of free fluid. The heart was greatly enlarged, both right and left ventricles being affected.

Tricuspid valve: Typical line of minute vegetations.

Mitral valve: Minute vegetations with older fibrous thickening.

Aortic valve: Many minute vegetations with older fibrous thickening.

Pulmonary valve: Apparently healthy.

Kidneys: Both organs showed chronic venous congestion. No evidence of meningitis was found, and the brain, middle ears and accessory sinuses appeared healthy.

Cultural Results :

Heart blood	Tubes 1 and 2. No growth.
Tricuspid valve ..	Tube 1. Hæmolytic streptococci, type 6. Tube 2. No growth.
Mitral valve	Tube 1. Hæmolytic streptococci, type 6, and *B. coli.* Tube 2. Hæmolytic streptococci, type 6.
Aortic valve	Tube 1. Hæmolytic streptococci, type 6. Tube 2. Hæmolytic streptococci, type 6.
Pulmonary valve ..	Tubes 1 and 2. No growth.

Microscopic Examination.—Sections of mitral and aortic valves showed typical rheumatic, non-ulcerative vegetations with little cellular response. No organisms were seen in sections stained by Gram's method.

CASE 5.—T. T., male, aged four years.

Clinical Diagnosis.—Acute polyarthritis and endocarditis.

Clinical Features.—Within six weeks of scarlatina the patient, who had appeared to have completely recovered, suddenly became ill with pyrexia and swelling of several joints, which were painful and extremely tender. Endocarditis supervened with a fatal result.

Post-mortem Findings.—The pleural cavity contained 5 c.c. serous fluid. The pericardial sac was dry, the walls being adherent with recently formed exudate. The left ventricle was considerably dilated.

Tricuspid valve: A number of minute rheumatic vegetations were present.

Mitral valve: A large number of recent vegetations bordered the free edge.

Aortic and pulmonary valves: Apparently healthy.

The lower lobe of the left lung showed a pale infarct of some standing, being separated from neighbouring tissue by well-formed fibrous tissue. The right middle lobe was the seat of a chronic inflammatory process, with diffuse interstitial fibrosis, atrophy of alveoli, partial or complete obliteration of some bronchi and enlargement of others.

Cultural Results.—A post-mortem throat swab yielded *Streptococcus viridans*, pneumococci and *Staphylococcus albus*.

Heart blood	Tubes 1 and 2. No growth.
Tricuspid valve ..	Tubes 1 and 2. No growth.
Mitral valve	Tube 1. *Streptococcus viridans* in pure culture. Tube 2. *Streptococcus viridans* in pure culture.
Pulmonary valve ..	Tubes 1 and 2. *Streptococcus viridans* in pure culture.
Pericardial exudate ..	Tubes 1 and 2. No growth on culture.
Peritoneal fluid ..	Tubes 1 and 2. No growth on culture.

Microscopic Examination.—Sections of the left ventricle showed rheumatic nodules at a late stage. No organisms were seen in sections stained by Gram's method.

CASE 6.—N. P., male, aged six years.

Clinical Diagnosis.—Acute rheumatic fever.

Clinical Features.—This patient was admitted to hospital with a history of polyarthritis of only one week's duration. Acute endocarditis followed, and death occurred within three weeks of onset of symptoms.

Post-mortem Findings.—There was a large serous effusion on both sides of the thoracic cavity. A typical organising pericarditis was present, with only a small volume of free fluid.

Tricuspid valve: Apparently healthy.

Mitral valve: Minute rheumatic vegetations, with slight fibrous thickening, indicating that the lesions were probably of longer duration than the history indicated.

Aortic valve: As in the case of mitral valve.

Pulmonary valve: Apparently healthy.

Cultural Results.—In my absence Dr. A. R. Macgregor, Pathologist to the Royal Hospital for Sick Children, Edinburgh, made the primary cultures.

Pericardial fluid: Hæmolytic streptococci, type 2, and *Streptococcus viridans.*

Mitral valve: Hæmolytic streptococci, type 2, and *Streptococcus viridans.*

Microscopic Examination.—No organisms were seen in Gram-stained sections of pericardial exudate or mitral valve.

Case 7.—F. H., female, aged fourteen years.

Clinical Diagnosis.—Acute rheumatic endocarditis.

Clinical Features.—This patient had a severe attack of rheumatic fever. Convalescence was slow, and six months later she began to complain of breathlessness. A sudden exacerbation of the respiratory distress was followed by flitting pains in the limbs, and the reappearance of pyrexia. On admission to hospital she collapsed with marked tachycardia. A routine throat examination during life yielded hæmolytic streptococci, type 4.

Post-mortem Findings.—The pleural sacs contained considerable quantities of serous fluid. The pericardial cavity contained a small volume of free fluid, but there was no pericarditis.

Tricuspid valve: Rheumatic vegetations extended along the line of closure of all cusps.

Mitral valve: Many fresh vegetations were present.

Aortic valve: Many recent vegetations were present and, in addition, the fibrous thickening of an older lesion was noted.

There was no macroscopic evidence of subacute bacterial endocarditis.

Cultural Results :

Heart blood	Tube 1. No growth. Tube 2. No growth.
Tricuspid valve ..	Tube 1. Hæmolytic streptococci, type 14, isolated. Tube 2. Hæmolytic streptococci, type 14, isolated.
Mitral valve	Tubes 1 and 2. Hæmolytic streptococci, type 14, isolated.
Aortic valve	Tube 1. Hæmolytic streptococci, type 14, isolated.
Pulmonary valve ..	Tubes 1 and 2. No growth.

Microscopic Examination.—Sections of aortic, mitral and tricuspid valves showed recent rheumatic vegetations, and many Aschoff nodules throughout the heart muscle. No organisms were seen in Gram-stained films.

Case 8.—W. P., female, aged nine years.

Clinical Diagnosis.—Rheumatic endocarditis and chorea.

Clinical Features.—The initial symptoms in this case were those of chorea. After slight trauma of the knee following a fall from a car, patient returned to school, but was sent home because of sickness and "raving." She commenced to kick her right foot against objects, and violent shrugging movements of the right shoulder followed. Later the left side of the body became involved. Acute endocarditis then developed, and at this stage hæmolytic streptococci, type 1, were isolated from the throat. Death occurred within three weeks of the onset of endocarditis.

Post-mortem Findings.—The serous sacs were all apparently healthy.

Tricuspid valve: No lesions were detected.

Mitral valve: Numerous minute lesions were present along the line of closure.

Aortic valve: A few vegetations along the ventricular aspect.

Pulmonary valve: Apparently healthy.

Cultural Results:

Heart blood ..	..	Tubes 1 and 2. No growth.
Tricuspid valve	..	Tubes 1 and 2. No growth.
Mitral valve ..	..	Tubes 1 and 2. Hæmolytic streptococci, type 1.
Aortic valve ..	..	Tubes 1 and 2. No growth.
Pulmonary valve	..	Tubes 1 and 2. No growth.

Microscopic Examination.—Sections of the left and right sides of heart were thoroughly examined, but no Aschoff bodies were seen. No specific or focal changes in the brain were found other than hyperæmia and ganglion cell chromatolysis.

No organisms were seen in Gram-stained sections of heart valve and muscle.

Case 9.—E. S., female, aged nine years.

Clinical Diagnosis.—This patient was admitted to hospital with a history of pyrexia and flitting pains in the joints. On admission an active heart lesion was already present. She was later sent to a convalescent home with mitral and aortic incompetence. An attack of tonsillitis preceded a relapse, and she was readmitted to hospital with severe præcordial pain, but no evidence of endocarditis. No hæmolytic streptococci were recovered from the throat. Signs of consolidation of the left lower lobe appeared, and a terminal broncho-pneumonia hastened death.

Post-mortem Findings.—The serous sacs all contained an excess of clear fluid, but there was no pericarditis. The heart was much enlarged, being both dilated and hypertrophied.

Tricuspid valve: Apparently healthy.

Mitral valve: Almost completely encircled by recent small vegetations.

Aortic valve: Several recent vegetations present, and also some older thickening of the cusps.

Pulmonary valve: Apparently healthy.

Cultural Results:

Heart blood ..	..	Tubes 1 and 2. No growth.
Tricuspid valve	..	Tubes 1 and 2. No growth.
Mitral valve ..	..	Tube 1. Hæmolytic streptococci, type 1. Tube 2. No growth.
Aortic valve ..	..	Tubes 1 and 2. No growth.

Microscopical Examination.—Numerous Aschoff bodies were seen in the interlobular septa of the myocardium, but no organisms were found in Gram-stained sections.

Summarising the above results, Table I. shows that from eight of this series of nine cases of rheumatic carditis hæmolytic streptococci were recovered from the heart valves with vegetations and from the pericardial lesions. This organism was

TABLE I.—RESULTS OF POST-MORTEM BACTERIOLOGICAL EXAMINATION ON NINE CONSECUTIVE CASES OF RHEUMATIC CARDITIS

Case.	*Clinical Diagnosis.*	*Pathological State and Result of Culture.*							*Notes.*
		Tube.	*Heart Blood.*	*Tricuspid Valve.*	*Mitral Valve.*	*Aortic Valve.*	*Pulmonary Valve.*	*Pericardium.*	
1	Acute rheumatic endocarditis			+	+	−	−	+	Hæmolytic streptococci, type 27, isolated from throat during life.
		1	*B. coli*	Hæmolytic streptococci, type 27	Hæmolytic streptococci, type 27	No growth	*B. coli*	Hæmolytic streptococci, type 27	
		2	*B. coli*	*B. coli*	Hæmolytic streptococci, type 27, and *B. coli*	No growth	No growth	Hæmolytic streptococci, type 27	
		3		No growth	*B. coli*	No growth			
2	Mitral stenosis and incompetence			−	+	−	−	+	Hæmolytic streptococci, type 14, isolated from throat during life.
		1	No growth	No growth	Hæmolytic streptococci, type 14, and *B. coli*	*B. coli*		Hæmolytic streptococci, type 14	
		2	No growth	No growth	*B. coli*	No growth		Hæmolytic streptococci, type 14	
		3			No growth				
3	Acute rheumatic fever			−	+	+	−	+	Hæmolytic streptococci, type 18, isolated from throat during life.
		1	*B. coli*	No growth	Hæmolytic streptococci, type 18, and *B. coli*	Hæmolytic streptococci, type 18, and *B. coli*	*B. coli*	Hæmolytic streptococci, type 18	
		2	*B. coli*	No growth	Hæmolytic streptococci, type 18, and *B. coli*	Hæmolytic streptococci, type 18, and *B. coli*	*B. coli*	Hæmolytic streptococci, type 18	
		3	No growth						
4	Rheumatic endocarditis			+	+	+	−	+	
		1	No growth	Hæmolytic streptococci, type 6	Hæmolytic streptococci, type 6, and *B. coli*	Hæmolytic streptococci, type 6	No growth	No growth	
		2	No growth	No growth	Hæmolytic streptococci, type 6	Hæmolytic streptococci, type 6	No growth	No growth	

				streptococci, type 6	streptococci, type 6, and *P. coli*	streptococci, type 6			
		2	No growth	No growth	Hæmolytic streptococci, type 6	Hæmolytic streptococci, type 6	No growth	No growth	
5	Acute polyarthritis and endocarditis	1	No growth	No growth	+ *Streptococcus viridans*	−	− *Streptococcus viridans*	+ No growth	Pneumococci, *Streptococcus viridans* and *Staphylococcus albus*, isolated on culture from throat at post-mortem.
		2	No growth	No growth	*Streptococcus viridans*		*Streptococcus viridans*	No growth	
6	Acute rheumatic fever				+ Hæmolytic streptococci, type 2, and *Streptococcus viridans*	+	−	+	
7	Acute rheumatic fever	1	No growth	+ Hæmolytic streptococci, type 4	+ Hæmolytic streptococci, type 4	+ Hæmolytic streptococci, type 4	− No growth	−	Hæmolytic streptococci, type 4, isolated from throat during life.
		2	No growth	Hæmolytic streptococci, type 4	Hæmolytic streptococci, type 4	No growth	No growth		
8	Rheumatic endocarditis	1	No growth	− No growth	+ Hæmolytic streptococci, type 1	+ No growth	− No growth	−	Hæmolytic streptococci, type 1, isolated from throat during life.
		2	No growth	No growth	Hæmolytic streptococci, type 1	No growth	No growth		
9	Subacute rheumatism	1	No growth	− No growth	+ Hæmolytic streptococci, type 1	+ No growth	−	−	
		2	No growth	No growth	No growth	No growth			

+ = macroscopic lesions of recent origin present. − = no macroscopic lesions of recent origin present.

present in pure culture in seven valves. In six others coliform organisms were also present, and in one case *Streptococcus viridans* and *Streptococcus hæmolyticus* were both obtained. No growth was obtained from three of the remaining five valves with vegetations, one yielded *Streptococcus viridans*, and one was not cultured. As controls, twelve valves without macroscopic lesions from these same hearts were cultured, and in no instance were hæmolytic streptococci recovered. Coliform organisms were obtained in three valve cultures and *Streptococcus viridans* in one, the remaining eight being sterile. The heart blood was sterile in six cases of the rheumatic series, coliform organisms were present in two, and in one instance this control was omitted.

NON-RHEUMATIC SERIES.—The results obtained in the twenty-two non-rheumatic cases are summarised in Table II. Coliform organisms and hæmolytic streptococci were both recovered from the heart valves of a case of post-operative peritonitis, while in one case of broncho-pneumonia hæmolytic streptococci were obtained in pure culture from the heart blood and heart valves. In both cases the pericardial cultures remained sterile, and *all* the heart-valve cultures yielded growths of hæmolytic streptococci. As the valve inocula were not washed free of blood, the presence of hæmolytic streptococci was attributed to traces of infected blood on the valve surfaces.

TABLE II.—RESULTS OF POST-MORTEM BACTERIOLOGICAL EXAMINATION OF TWENTY-TWO NON-RHEUMATIC CONTROL CASES.

Number of Cases.	*Result of Culture.*		
	Heart Blood.	*Heart Valves.*	*Pericardium.*
15	Sterile	Sterile	Sterile.
3	Coliform organisms	Sterile	Sterile.
2	Coliform organisms	Coliform organisms	Sterile.
1	Coliform organisms and hæmolytic streptococci	Coliform organisms and hæmolytic streptococci	Sterile.
1	Hæmolytic streptococci	Hæmolytic streptococci	Sterile.

Discussion

The distribution of hæmolytic streptococci in cultures from rheumatic and non-rheumatic hearts in the above series was striking. Unless a phenomenal chance distribution of hæmolytic streptococci in the heart valves of the various cases were postulated, the results indicated that agonal or post-mortem blood invasion did not explain the appearance of hæmolytic streptococci in only valves with macroscopic lesions. Coliform organisms were also isolated under the same conditions, but were found in the heart blood and in cultures from both healthy and diseased valves. Careful examination of serial sections of vegetations excluded the possibility that the positive findings were the result of subacute bacterial endocarditis. The pathological manifestations were entirely those of rheumatic endocarditis, and no organisms were found in sections stained by the routine Gram's method. Any possibility that the presence of hæmolytic streptococci was the result of contamination from some source other than the tissues of the bodies under examination was completely excluded by the fact that in five cases the streptococcus recovered from the cardiac lesion, in the individual case, was of the same serological type as the strain isolated from the patient's throat before death. Further, in those cases where hæmolytic streptococci were isolated from more than one valve the strains were serologically identical. Indirect evidence has already been reported as to the part played by hæmolytic streptococci in acute rheumatic infections by Green, 1938 (*a*) (*b*). The observations now presented greatly strengthen this association, and strongly support the view that these organisms bear a causal relationship to the lesions of the disease. Although the number of cases in this series is too limited to be conclusive, they are recorded in order to encourage further work on the same lines.

Summary and Conclusions

1. The pericardial and valvular lesions in nine cases of acute rheumatic endocarditis were examined bacteriologically.

2. Hæmolytic streptococci were cultivated from valves with macroscopic lesions in eight cases, and *Streptococcus viridans* in one case.

3. Hæmolytic streptococci could not be cultivated from valves without macroscopic lesions, nor from heart blood, in the same cases.

4. In five cases hæmolytic streptococci were recovered from the throat during life, and in each case the strain was serologically identical with that isolated from the cardiac lesions.

5. Hæmolytic streptococci were cultivated from both heart blood and heart valves in two of twenty-two non-rheumatic control cases.

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THE INFLUENCE OF MORPHOLOGICAL STRUCTURE ON THE PATHOLOGY OF JOINTS

By R. G. ABERCROMBIE

NOTWITHSTANDING the great diversity of arthritic conditions, each joint in the body possesses a character of its own in its response to the invasion of morbid processes. This is partly due to the special mechanical factors of each particular joint, and partly to the morphological structure which is the heritage of its evolutionary history.

Human anatomy may be regarded as the contemporary phase of a long series of modifications and adaptations of function and of form which have left their traces upon every organ and structure of the body. With regard to the skeleton and the motor structures generally, the all-important transition is that which has led to the assumption of the erect posture, for this transition is comparatively recent in time and has involved far-reaching changes in the architecture and the mechanism of the bones, joints, muscles, and ligaments.

The attempt to unravel the ancestry of the human race may be compared to the attempt to trace the genealogy of an individual man. The first few generations in the lineage of an individual may be traced backwards with confidence. As we follow the line of descent still further into the past, it becomes progressively more obscure. Nevertheless, from a variety of considerations we may still obtain a general idea as to the remote origin and the stock from which the family arose. Similarly, with regard to the evolution of the human species there is a general agreement as to the more recent stages, but the more remotely the line is traced, the more debatable does it become.

Our knowledge of man's ancestry is largely derived from the geological record. Light is also thrown on the problem by the study of embryology and development, for the "Law of Recapitulation" states that each individual during its development passes through the successive phases which the race to which it belongs has passed through during its evolution. A further

sidelight is obtained from the study of existing forms of life which are presumed to bear a resemblance to ancestral types now extinct.

As the result of all these lines of investigation, it is generally believed that the human species is descended from a prehuman type which had much of the character of the anthropoid apes of today. Beyond that point the lineage becomes obscure. It is surmised that earlier progenitors were of an ape-like form whose habitual posture approximated to the quadrupedal, and that a still more remote ancestor was of a prosimian type comparable to the present-day tarsier. Although it may well be believed that the convergence of the eyes in the prosimian ancestry resembled that seen in the tarsier, it is probable that the resemblance of bodily structure was only of a general nature, for the existing tarsier is a highly specialised animal with strangely elongated tarsal bones. Since the dentition of the tarsier is insectivorous, it has been conjectured that man's remote prosimian ancestor was derived from the insectivores, perhaps from some type resembling the tupaia or tree-shrew, and earlier still from a marsupial. Man's lineage is thus conjecturally traced backwards through the anthropoid type to the prosimian and beyond that to the quadruped. Imperfect though our knowledge is, it is yet sufficient to add interest to the study of the pathology of the joints, for the sequence of evolutionary development has an influence on the sequence of pathological events.

It is a generally accepted principle that it is the most recently acquired characters that are the most precarious in their tenure when exposed to the influence of disease. A similar principle is expressed by the "Law of Dissolution" in pharmacology, which states that the toxic effects of such substances as alcohol and chloroform first impair those functions which have been the last to appear in the history of the species, and that as the toxic effects progressively increase, less recently acquired functions are affected in order of succession, the most primitive functions being affected last of all. Comparable effects may sometimes be observed as the result of the gradual encroachments of a progressive morbid process upon the structure and function of joints. The advance of a chronic disease may thus reproduce, in a reverse order, the successive phases which the affected structures have passed through during the course of their evolution. To this process the term *retrogression* may be applied.

In order to apply these ideas to the pathology of a particular joint—the shoulder-joint, for example—it is necessary to consider the characters of the joint in question as exemplified in a series of existing animals, each one of which typifies a stage in human evolution. Such a series is constituted by the quadruped, the prosimian, the anthropoid and man.

In the quadrupedal type in general the head of the humerus is relatively small, and is proportionate to the size of the glenoid cavity. It is connected with the shaft by a well-defined anatomical neck. The articular surface is restricted in size, oval in form and antero-posterior in direction, and is thus specially adapted to the movements of flexion and extension. Abduction is poorly provided for by the shape of the joint surfaces and is imperfectly accomplished by movements of the scapula on the chest wall.

In the prosimians the head of the humerus is larger in relation to the size of the glenoid cavity, the anatomical neck is less defined, and the articular surface of the head is more extensive. More abduction is possible than in the quadruped, and in some species it is performed freely; but from the form of the skeleton it appears to be chiefly carried out by movements of the scapula upon the thorax rather than by movement at the shoulder-joint. Little information is to be obtained from the shoulder-joint of the tarsier, for it is imperfectly developed and specialised for certain peculiar movements. In the lower monkeys the general characters of the joint still have a quadrupedal character; abduction appears to be performed partly at the joint itself and partly by scapular movement, reinforced by nimble sideways movements of the whole trunk.

In the anthropoid apes the transformation to the human type of shoulder is complete. The head of the humerus is disproportionately large in relation to the glenoid cavity; it is hemispherical in form and the anatomical neck is obscured. The extensive articular surface allows for an extremely wide range of movement, including abduction. In the gibbon, abduction appears to be more developed than in man, so that the animal moves its upper limbs in every direction with the utmost freedom, without adjustment of the position of its trunk. A clue to the ancestry is provided by the observation that in the skeleton of the immature chimpanzee the head of the humerus is of distinctly quadrupedal type, and if a juvenile chimpanzee is watched at play the deficiency of abduction is clearly apparent.

In the human embryo the head of the humerus is also of quadrupedal form.*

The structure of the shoulder-joint in man resembles that of the anthropoid apes, but there is a distinction with regard to function. In the ape the grasping and "handling" of objects is distributed amongst all four limbs; in man the lower limbs are degraded to the position of pediments, and all exact movements are performed by the upper. The special functions of man's shoulder are thus not only recently acquired, but are subjected to the strain of continuous usage.

The characters of the shoulder-joint, as studied in the quadruped, the prosimian, the anthropoid, and finally in man, thus represent a series of modifications whereby an articulation adapted to carry the weight of the body has been gradually transformed into a highly mobile joint well fitted to execute varied and accurate movements, including abduction at the shoulder-joint itself. Abduction at the shoulder-joint is of importance in that it confers upon the movements of the upper limb an accuracy far greater than can be attained by similar movements carried out by the rotation of the scapula or by adjustment of the position of the trunk. The advance in articular abduction is thus an advance in accuracy of movement.

In man, both types of abduction come into play. The movement of the arm from the position of adduction through ninety degrees to that of horizontal abduction is carried out at the shoulder-joint, whereas the movement through the ensuing ninety degrees to the vertical is effected by rotation of the scapula. Extreme extension also entails a change in the position of the scapula, though this is small in degree compared to that associated with extreme abduction. Accurate movements of the upper extremity in man are best performed with the limb in a position below that of the horizontal, where they are controlled by the shoulder-joint; whereas movements performed with the limb in the position above the horizontal are controlled by the more primitive rotation of the scapula and are in consequence clumsy in character.

The shoulder-joint affords a good illustration of the influence of the evolutionary sequence upon pathology, and it is therefore

* The above observations are largely based on the study of the excellent osteological series illustrating the ancestry of man in the Western Park Museum, Sheffield.

of interest to consider in detail the morbid conditions to which it is subject. Since abduction at the joint itself is a recently acquired function, the muscles which subserve this movement are particularly liable to suffer from the effects of injury or disease. Paralysis of the deltoid often occurs as the result of an injury to the circumflex nerve or a toxic neuritis; and both the deltoid and the supraspinatus are frequently affected in acute anterior poliomyelitis, in birth paralysis and in traction paralysis of the brachial plexus. The tendon of the supraspinatus may become the seat of a degenerative or inflammatory process, particularly where it is related to the subacromial bursa, and the same tendon occasionally suffers rupture. The deltoid is often the subject of muscular rheumatism, and its insertion into the humerus is a frequent site of tenderness, due either to a rheumatic or fibrositic process or as the result of strain.

The periarticular fibrous and connective tissues about the shoulder have undergone structural modifications which increase their pliability and mobility, and thus facilitate the newly acquired and complex muscular movements. These recent changes in the connective tissues are insecure in their tenure. As the result of a large number of diverse pathological influences they tend to retrogression, and thus give rise to a painful and progressive stiffness of the shoulder-joint. Several names have been suggested for this condition, such as "scapulo-humeral periarthritis" (Douthwaite); "frozen shoulder" (Codman); "Duplay's disease," from the name of the author who first accurately described the condition. "Periarticular fibrositis of the shoulder" is here suggested as an appropriate designation, the term *fibrositis* being included for reasons which will appear later.

The various pathological conditions which may give rise to the condition are as follows:

1. Trauma; direct injuries or strains of the joint itself or of its neighbourhood.

2. Rheumatism, using the term in its most general sense, including general arthritic conditions and menopausal rheumatism.

3. Infective conditions, such as pneumonia, influenza, tonsillitis and cholecystitis. Latent infections also sometimes appear to operate as a cause.

4. Neuropathic conditions. In hemiplegia, obscure trophic

influences associated with the disuse may give rise to painful stiffness of the shoulder.

5. Debility, chronic ill-health, cachexia, severe anæmia, metabolic affections, such as glycosuria or gout.

6. Immobility or inaction from any cause. For example, when plaster-of-Paris splinting has been used for fracture of any part of the upper extremity, the shoulder may remain troublesome for long after the recovery of the fracture.

The pathological causation is thus very diverse, but with regard to the affection of the shoulder-joint the cases resemble each other closely in their symptoms, physical signs and clinical course; it is therefore a fair assumption that though the pathology is diverse, the morbid anatomy is a constant one. Our knowledge of the morbid anatomy is largely based on an autopsy described by Duplay and quoted by Douthwaite (*B.M.J.*, February 26, 1938).

The case had been treated by Duplay for a periarthritis of the shoulder following an injury. The result was good, but the patient died two months later of pneumonia. The results of the autopsy thus disclosed the vestiges of the morbid condition rather than its active phase. " On the affected side the deltoid was paler than normal; the subdeltoid tissue was fibrous, exhibiting dense bands running to the upper end of the humerus. The subacromial bursa was obliterated. The tendons of the supra- and infraspinati had lost their polish, as had also the inferior surface of the acromion. It was evident that the subacromial bursitis was the chief lesion, with extension to neighbouring structures. There could be seen ruptured adhesions on the inferior surface of the deltoid. The articular capsule was somewhat thickened, but the articular surfaces were quite normal." It is clear that the morbid process had been essentially a periarticular fibrositis affecting the connective tissues surrounding the joint, but not the articulation itself. This accords with the clinical evidence, for the skiagraphic appearances of the bones are normal, there is no crepitus on movement, and muscular wasting is slight or absent. Further evidence of a widespread fibrositic process is afforded during the acute phase by the presence of points of tenderness, the most usual sites being the insertion of the deltoid, the tip of the coracoid process and the supra- and infraspinous fossæ. The subacromial bursa, a structure subserving the recently acquired abduction, is frequently

but not invariably affected. Since no swelling occurs, either of the bursa or elsewhere, the process appears to partake as much of a degenerative as of an inflammatory character.

The existence of a dual or alternative mechanism for the movements of the shoulder, particularly abduction, explains the insidious manner in which the impairment of movement often occurs. The first slight loss of articular movement is easily compensated for by the more primitive mechanism of scapula movements, and thus may pass unnoticed; once initiated, the process tends to progress, greater proportions of the movements being gradually transferred to the scapula without the patient's knowledge. Finally, a degree of stiffness is reached which cannot be compensated for by scapular movements, and the patient finds to his surprise that he is unable to perform some such action as putting his hand in his pocket. (In such a joint as the elbow, for the sake of comparison, flexion and extension must be performed at the joint itself or not at all, and thus the natural movements tend to check the progress of an insidious ankylosing process.)

Each successive phase in the loss of movement represents a stage in retrogression. During the first phase, abduction at the shoulder-joint is impaired and is transferred to movements of the scapula, so that at this stage the patient is in the condition of a prosimian. As the process advances, abduction at the shoulder-joint is abolished altogether, and the loss can no longer be compensated by the scapular movements; although abduction is lost, the patient can still perform flexion and extension, so that at this stage he is in the condition of a quadruped.

These observations have a bearing on the treatment. If a patient whose arm is in the quadrupedal condition attempts to move the limb while he retains the ordinary human posture, sitting or standing, his efforts are both difficult and painful; whereas if he adopts the posture of a quadruped, the movements are easy and painless. To utilise this in practice, the patient should support himself by placing his sound forearm and hand on the edge of a table, and should flex the trunk forwards at the hips, the affected limb being allowed to dangle vertically downwards. In this quadrupedal position he should swing his dangling arm, gently at first, and more freely as the range of movement improves. Flexion and extension are first performed, and abduction, adduction and circumduction are gradually added,

all the movements being aided by the pendulum-like swing of the pendent arm. Since the patient himself regulates the range of the movements, they are painless. With improvement in abduction, the later stages of treatment are carried out in the ordinary sitting or standing posture.

Another method of treatment may be alluded to, since it also depends on pathological considerations. The loss of pliability in the connective tissues impairs the normal laxity of the joint and thus impedes its natural play. Improvement may often be obtained by the simple process of stretching the affected tissues. The patient's position being fixed by some simple device, the manipulator grasps the hand of the affected limb and brings the arm into the position of abduction. Steady traction is then made upon the hand, thus bringing all the structures about the shoulder into a state of tension. No movements should be used, and care should be taken to relax the tension gradually, or pain will ensue. It is not necessary to discuss here the value of the various methods of physical treatment, or of forced movements under anæsthesia; all such methods have their place in the treatment of suitably selected cases. The essential object of treatment is to restore the movements of the joint, for the restoration of movement is associated with a regeneration of the normal structure and function of the connective tissues. Immobilisation may be advisable for a period during the acute phase, but it should not be too prolonged.

The shoulder-joint is occasionally the subject of osteo-arthritis. This condition is far less frequent than periarticular fibrositis, and clinically the two conditions form a complete contrast. In the osteo-arthritic condition the limitation of movement is usually of only moderate grade, creaking and crackling are present on movement, muscular wasting is well marked, the X-ray examination frequently discloses an irregularity of the bones, sometimes associated with the presence of minute osteophytes, the pain is often characteristically nocturnal, and the treatment required is of a lenitive character. Rarely periarticular fibrositis may coexist with an osteo-arthritic condition. Osteo-arthritis of the shoulder is most usually seen in elderly subjects, particularly those engaged in laborious occupations, and it not infrequently follows trauma. It may be regarded as a degenerative process akin to the similar affection of the hip-joint.

The evolutionary history of the hip-joint differs widely from that of the shoulder, and it is therefore in accordance with expectation that the pathological reactions of the two structures should be dissimilar. The hip-joint in man retains its primitive functions of transmitting the weight of the body to the lower limbs and of subserving locomotion. These functions, however, have undergone modification in one respect: in the quadruped the functions in question are distributed amongst all four limbs, whereas in the prosimian, and to a still further extent in the anthropoid, they are largely relegated to the lower limbs. In man this specialisation is carried a stage further, so that the whole onus of weight-carrying and of locomotion falls upon the lower limbs, and in consequence upon the hip-joints. Hypertrophic changes, osteophytes and osteo-arthritis provide the evidence of the instability of a recent adaptation, and may be regarded as Nature's efforts to buttress up structures which are unequal to the strains to which they are subjected. Osteo-arthritis, tuberculosis, osteo-chondritis juvenilis (Perthes' disease), slipping of the epiphysis and coxa vara are all associated either directly or indirectly with strain or trauma, and all are usual affections of the hip-joint, whereas similar or comparable conditions are much more rare in relation to the shoulder. In the hip the recent modification has been in the direction of increased stress, and the characteristic morbid changes are to be found in the bones and the joint itself; whereas in the shoulder the recent modification has been in the direction of increased mobility, and the characteristic morbid changes affect the connective tissues subserving this advance.

The transition in bodily posture from the horizontal to the vertical has been brought about by a modification of the architectural curvature of the vertebral column, and the chief element in this change has been the development of a curve with the convexity forwards in the lumbar region. In the prosimian the thoracic and lumbar vertebræ form a single large arch with the convexity backwards, and in the lower monkeys the curvature is of similar type but of less degree. The first indication of a lumbar curve convex forwards is to be seen in the anthropoid apes; it is faintly present in the skeleton of the orang-utang, distinctly visible in the gorilla, and in the chimpanzee there is an approximation to the human character of spine, with a sigmoid curve convex backwards in the thoracic and convex forwards

in the lumbar region. In man the lumbar spine is strongly arched with the convexity forwards, so that the backward inclination of the upper limb of the arch carries the trunk backwards into the fully erect posture.

The successive modifications of posture have been associated with successive redistributions of stress. In the quadruped and the prosimian the weight of the body is distributed over the whole length of the spine; in the anthropoid it falls in a large proportion on the lumbar region, and in man the whole weight of the head, the upper limbs and the trunk is ultimately transmitted through the lower lumbar vertebræ.

Man's lumbar spine is thus subjected to the twofold modification of increased curvature and additional stress. The great variability of its structure indicates that it is still undergoing adaptive differentiation, and that its contemporary phase is one of plastic evolution. No other region of the body exhibits so gross a range of variation. The vertebræ which compose it may vary in number; the fifth may have a partially sacral character; the bodies or the laminæ may be imperfectly developed; the lateral processes may be detached; and the individual vertebræ, particularly the fifth, vary in magnitude and shape.

The variability of structure is associated with instability of function, which is expressed in the form of the symptoms of disease. Pain in the lower part of the back is one of the most frequent of human complaints. The symptoms may have many origins and may take many forms, physical and psychological. The lumbar spine is the most frequent site in the body for osteo-arthritis; the adjacent muscles are the subjects of myalgia, and the connective tissues of fibrositis; lumbar and sacro-iliac subluxations and strains are often the legacies of slight developmental defects; and in debility and abnormal psychological states the maintenance of the curvature may rise into consciousness in the form of pain.

The shoulder, the hip and the spine have been taken as examples to illustrate the influence of evolutionary history and morphology upon pathology; and in many other regions of the body similar considerations serve to elucidate phenomena which would be otherwise anomalous and obscure.

RECENT RESEARCHES ON ARTHRITIS AND RHEUMATISM IN THE UNITED STATES*

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Among chronic diseases in the United States "rheumatism" ranks first in prevalence, second in producing disability, second in producing invalidity (permanent disability) and fourteenth in causing death. Among the 127,000,000 persons in the United States there are 6,850,000 with "rheumatism," considerably more than the combined figures of those with heart disease (3,700,000 cases), cancer and other tumours (930,000 cases), tuberculosis (680,000 cases) and diabetes (660,000 cases) altogether. Such were the figures obtained in a recent National Health Survey[1] in which "rheumatism included arthritis, gout, neuralgia, neuritis, lumbago, etc." Another survey reported that there were annually disabled about 1,500,000 Americans with "arthritis," and an additional 1,750,000 persons with neuralgia, neuritis and lumbago.[2] These figures again indicate the enormous morbidity produced by the "rheumatic diseases."

Gonorrhœal Arthritis

In the United States there are annually about 1,037,000 cases of acute, and about an equal number of cases of chronic, gonorrhœa.[3] Recent statistics indicate that about 1 to 3 per cent. of such patients develop gonorrhœal arthritis.[4]

Diagnosis.—Since the newer forms of treatment of gonorrhœa and gonorrhœal arthritis are so highly successful it is more important than ever to make the diagnosis in such cases early and promptly in order to prevent the gross articular destruction that might otherwise result from delayed treatment. Suggested criteria [5, 6] for a diagnosis of "proved gonorrhœal arthritis" are: (1) a history of recent or existing gonorrhœa, (2) clinical evidence of genital gonorrhœa, (3) isolation of gonococci from a primary

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focus, (4) the presence of acute or subacute joint disease having the recognised clinical characteristics of gonorrhœal arthritis, (5) demonstration of gonococci in synovial fluid, (6) a positive gonococcal complement-fixation test on blood or synovial fluid, or both. In certain cases a positive diagnosis of gonorrhœal arthritis is made by the isolation of gonococci from joint fluid or tissues even in the absence of several or all of the other criteria noted. A diagnosis of " probable gonorrhœal arthritis " is justified even in the absence of points (5) and (6), when the first four criteria are present, particularly if the patient makes a prompt response to a therapeutic test with sulphanilamide or artificial fever.

The clinical characteristics of several large new series of cases of proved gonorrhœal arthritis were presented.[5-7] A curious feature was noted: respiratory symptoms, apparently a part of the systemic toxæmia, often preceded the arthritis; in connection with febrile polyarthritis this often led to an erroneous diagnosis of rheumatic fever. Recently stressed as a feature of some diagnostic importance in systemic gonorrhœa were skin lesions, described [5, 8-11] as scattered petechiæ (small red sore spots or slightly tender, circumscribed, purplish-red areas, 2 mm. to 1 cm. in diameter, chiefly on extremities, many having a central white area of necrosis, a few with vesiculation and sero-purulent fluid), or as an eruption (maculo-papular, in some areas hæmorrhagic, rapidly becoming vesicular, then pustular). Such lesions were generally associated with frank gonococcæmia, with or without endocarditis.

Since about 80 per cent. of gonococcal complement-fixation tests done in their cases of proved gonorrhœal arthritis were positive, some [5, 6, 12] considered the test an important diagnostic aid; others,[13] however, considered it unreliable because false positive tests often were obtained on patients without gonorrhœa. Bactericidal antibodies against gonococci appear in blood and in synovial fluid of patients who have gonorrhœal arthritis with sterile joint fluid and without gonococcæmia. Such antibodies, however, are low or absent in blood and synovial fluid of patients with infected joint fluid or with gonococcæmia.[14] Thus the prevention of bacteræmia seems to depend on the antibody content of blood or on an efficient local defence reaction in the primary focus of infection. Gonococci tend to localise and survive in regions amply supplied with mucin (urethra, cervix, conjunctiva, joints). Synovial mucin assists some strains of

gonococci to survive when synovial fluid antibodies are low, but not when they are high.[14]

TREATMENT.—Until the advent of sulphonamide compounds, induced fever constituted the most promptly effective treatment ever devised for gonorrhœa and gonorrhœal arthritis. Although fever therapy has been largely (but not completely) supplanted by the use of sulphanilamide no one should discount the extremely valuable, highly scientific and courageous pioneer work of those who collaborated in its development. Further experiences have amply shown that fever therapy provides a potent weapon against gonococcal infections. In the literature reviewed for this survey about a dozen new reports presented the results of fever therapy in about 350 cases of gonorrhœal arthritis.[4, 15-23] Prompt cure was obtained in about 75 to 90 per cent. of all cases in which it was employed. Best results were noted in the more acute cases, in which treatment was begun before irreparable articular damage had had time to occur. In most cases the genital lesions also responded satisfactorily to fever therapy, but in the treatment of females superior results were noted from "combined heating"; this term denotes systemic fever produced by fever cabinets or short-wave diathermy and additional heating of the pelvis by the use of pelvic diathermy electrodes.[15, 16] Single long sessions of artificial fever, long enough to kill each patient's particular strain of gonococcus (average 14·8 hours at 41·5° C.) were recommended by some[16, 22, 23] to accomplish "one-treatment cures."

Worthy of special note were two reports which[24, 25] compared the results of fever therapy for gonorrhœa and gonorrhœal arthritis with those from older methods of treatment (physical therapy to joints; local chemotherapy to genital lesions). Cures were obtained in 76 per cent. of cases of acute gonorrhœal arthritis, and in 24 per cent. of cases in which chronic gonorrhœal arthritis was treated by fever, but cure resulted in only 8 per cent. and 5 per cent. respectively of a similar number of acute and of chronic cases in which treatment was by other methods. The average period of hospitalisation in the cases in which treatment was not by fever was just twice as long (forty-five days) in the acute cases and three and one-half times as long (156 days) in the chronic cases as it was in those in which treatment was by fever. In another series of cases of gonorrhœa with non-articular complications the percentage of patients cured by fever was definitely higher than those cured by older methods, and with fever therapy cures were

obtained in a third to a fourth of the time required by older methods.[25]

Minor complications (herpes, headaches, gastro-intestinal symptoms, tetany, mild burns) affected about 20 to 30 per cent. of patients subjected to fever therapy.[4, 26] Serious or fatal complications rarely occur when fever therapy is applied by a trained personnel. In 1937 only eleven deaths related to fever therapy were reported in connection with many thousands of sessions of fever; the mortality rate was less than 0·2 per cent. Some[27, 28] regarded anoxæmia as perhaps the chief cause of major complications, and for their prevention advocated administration of oxygen and carbon dioxide and avoidance of sodium amytal or epinephrine during sessions of fever.

The development of sulphonamide compounds and their application to the treatment of disease bids fair to rank among the great therapeutic advances. For one thing, it has established beyond all doubt that chemical " specifics " can be developed not only, as in the past, for non-bacterial (protozoan) infections, but also for microbic diseases. Physicians everywhere can well thrill to this chapter in medical research, a chapter which is still unfolding and which reveals a story of international co-operation that a sorry world of politics might well copy. Born of German chemical researches, the work has been developed and extended by physicians in many countries and of many nationalities, perhaps in particular in England, France and the United States. Those concerned with the care of patients with articular diseases should in particular familiarise themselves with the development of this work, because, as the work is being extended, it would appear that certain sulphonamide compounds can be successfully applied to the treatment not only of gonorrhœal arthritis, but also of the rarer but most troublesome articular lesions due to beta-hæmolytic streptococci, meningococci, pneumococci, perhaps also to *Brucella melitensis*, typhoid bacilli and other bacteria as well. Those interested may find a summary of the earlier work on prontosil and sulphanilamide (through 1937) in the *Fifth Rheumatism Review* just prepared for the American Rheumatism Association.[4]

Sulphanilamide was introduced to American physicians in January, 1937, by Long and Bliss, who in a series of papers [29-31] described its effects on experimental infections and on infections of human beings with beta-hæmolytic streptococci. They and others[4] soon applied the substance in the treatment of pneumo-

coccic and meningococcic infections, and in May, 1937, reports of its successful use in gonorrhœa were published almost simultaneously by Dees and Colston[32] and by Reuter.[33] The development by Marshall, Emerson and Cutting[34] of tests for the quantitative determination of sulphanilamide in body fluids and studies on its absorption and excretion led to more effective methods for its administration. The exact mode of action of the prontosils and of sulphanilamide is still obscure. The original idea that perhaps the prontosils were effective only in relation to their quantitative reduction to sulphanilamide does not satisfy some[4, 35] who have noted good results from sulphonamide compounds which cannot be reduced to sulphanilamide *in vivo*, and from amounts of prontosil solution which liberate only a few grains of sulphanilamide a day. Space cannot be given here for a review of the American reports on the toxic manifestations of sulphanilamide; in the review noted[4] these were described: sulphanilamide fever, the gastro-intestinal, renal and nervous symptoms, skin rashes, acidosis, leukopenia, acute hæmolytic anæmia, agranulocytosis, cyanosis, sulphæmoglobinæmia and methæmoglobinæmia. In general, sulphanilamide and related compounds are either nontoxic or only mildly toxic to man. Serious reactions occur only rarely. Among the first 4,000 cases reported, in which patients were treated with these compounds, only ten deaths apparently related to the drug occurred;[36] in five of them the drug may not have been the actual cause of death. Deaths occurred almost exclusively from agranulocytosis.[4] (This does not include the deaths from elixir of sulphanilamide Massengill, which were due, of course, not to the sulphanilamide, but to the solvent.)

Among the early patients with gonorrhœa treated with sulphanilamide were only a few with arthritis, but the results were "dramatic," "astonishing," prompt cures generally being noted.[32, 33, 37, 38] Several reports[4] on the effects of sulphanilamide in cases of gonorrhœa without arthritis appeared; when adequate doses were given, prompt cures were effected in 80 to 90 per cent. of cases. In some of the earlier cases inadequate doses were given. With experience, the tendency has been to use larger and more effective doses and to continue administration of the drug for a sufficient length of time to give more certainty of its complete effectiveness, rather than to reduce the dose or stop administration of the drug prematurely. In general the dose used has been that recommended by Long and Bliss[30] to obtain and maintain

an effective concentration of the drug in the blood (a daily dose of ¾ grain sulphanilamide per pound of body weight, with a constant intake of fluid).

Because of toxicity of the drug for certain patients, they cannot take sulphanilamide in effective amounts; other patients may be infected with strains of gonococci unusually resistant to the drug (as certain strains were found to be resistant to fever therapy). In some cases in which patients are resistant to sulphanilamide or to fever therapy alone the combination of sulphanilamide (40 to 80 grains daily) with one to three rather short sessions of fever (three to four hours at 103° or 104° F.) were reputedly successful.[39, 40] My colleagues and I[4] also have noted successes with this combination, which seems indicated primarily if patients are truly resistant to full doses of the drug, or are tolerant of only small doses. The combination of fever therapy and sulphanilamide also has been suggested for those patients who urgently need an immediate cure for domestic or economic reasons.

A few reports on older methods of treatment may be noted. Some investigators considered gonococcus vaccine[41] or auto-serotherapy[42] effective; others found the intra-articular injections of specific antigonococcal serum[43] and the use of Corbus-Ferry filtrate[44, 45] of little or no value.

Tuberculous Arthritis

The clinical features presented in 122 cases of juvenile tuberculous spondylitis were reported.[46] Tuberculosis affected the lungs in 60 per cent., joints in addition to those of the spinal column in 20 per cent. of the cases. Spinal lesions were cervical in 4 per cent., thoracic in 77 per cent., lumbar in 16 per cent., lumbo-sacral in 3 per cent. Abscesses afflicted 75 per cent., paraplegia 7 per cent. of the patients. Spontaneous intervertebral fusion, a rare event, occurred in six cases. Of the 122 patients, 16 per cent. died, often with amyloidosis. Some recent writers[46, 47] favoured prolonged conservative treatment (long immobilisation on a convex hyperextension frame) before performing fusion in cases of juvenile Pott's disease, an opinion in contrast to that of others who expressed the belief that much time and some lives can be saved by early fusion.

Pneumococcal Arthritis

Pneumococcal arthritis is rare. Among a series of 1,800 cases of pneumonia, only two cases of pneumococcal arthritis were encountered.[48] The condition generally accompanies pneumonia, but may accompany pneumococcal septicæmia without pneumonia. Monarthritis usually is present; articular function may be seriously impaired, or it may be completely restored if joints are adequately drained. Diagnosis rests on isolation of pneumococci from joints. A number of reports[4] indicate that sulphanilamide may be effective against certain types of pneumococcal infection. In particular, American physicians are awaiting with interest further reports on the value of sulphapyridine against pneumococci. If the preliminary English reports on its value are corroborated, pneumococcal arthritis may become even rarer than it is now.

Syphilis of Joints

A survey of recent literature on tabetic Charcot joints was made[49] to review their clinical features. Tabetic articular lesions usually are single and commonly affect lower extremities; an unusual case was reported, that of a man with multiple tabetic arthropathies. Charcot joints are not notably affected by antisyphilitic treatment, but some believe they may be prevented by fever therapy of early syphilis or early tabes.[4]

Articular Lesions from Brucellosis: Undulant (Malta) Fever

Symptoms referable to muscles and joints are common, sometimes dominant, features of brucellosis of man. They are often produced by caprine strains, less commonly by porcine, and rarely by bovine strains of Brucella. Arthralgia of varying severity affected 30 to 40 per cent. of recent American patients.[50-53] Migratory and polyarticular, the arthralgia was commonly misdiagnosed "rheumatic fever." Frank arthritis occurred only occasionally;[52] painful[54] and painless[50] hydrarthrosis was seen.

In the United States, between 1928 and 1934, 9,317 cases with 374 deaths were reported, evidence that the incidence of the disease or its recognition, or both, are rapidly increasing. These figures have been compared to European statistics.[55] Current

studies stress the fact that no type of fever is pathognomonic of the disease, fever is often absent, symptoms are multiple and physical findings are scarce; hence the dictum: "Think of brucellosis in all cases of prolonged ill-defined sickness, in all cases of unexplained fever, especially without localising signs, and in all cases of prolonged disability of the neurasthenic type."

Certification of the diagnosis rests on laboratory tests, which unfortunately are neither easy nor consistently helpful. Some expressed the belief that agglutination tests which are positive in any titre are indicative of disease and are more reliable than skin tests; others favoured the latter.[4]

Since spontaneous remissions and cures occur, therapy is difficult to evaluate. *Brucella abortus* vaccine seemed valuable to some,[56] of little value to others. Several patients appeared to be cured by the use of induced fever.[4] The worth of sulphanilamide and related compounds is being studied; final conclusions have not been reached.

Meningococcic Arthritis

American workers have confirmed the observation of their English colleagues that meningococcal infections, including those of joints, are amenable to treatment by sulphanilamide.[4, 57] Three cases of meningococcic arthritis in which treatment by sulphanilamide was successful were reported.[30, 58] Some[59] consider the combined use of serum and sulphanilamide superior to the use of either alone.

Articular Diseases due to Hæmolytic Streptococci

Since sulphanilamide has been found to be so effective against beta-hæmolytic streptococci, it is particularly important to recognise the bacteriologic identity of articular complications from such bacteria. Articular complications may occur with puerperal sepsis, scarlet fever, hæmolytic streptococcal osteomyelitis, streptococcic sore throat or otitis media, and hæmolytic streptococcæmia.[29, 30, 31] In a few cases of metastatic arthritis with puerperal sepsis,[60] hæmolytic streptococcæmia[61] and hæmolytic streptococcal meningitis,[62] cure by sulphanilamide has been reported.

Scarlatinal Arthritis

Three articular complications of scarlet fever are recognised: type 1, non-suppurative scarlatinal arthritis with sterile exudates; type 2, suppurative scarlatinal arthritis with hæmolytic streptococci in purulent exudates; type 3, scarlatinal or post-scarlatinal rheumatism, in reality the polyarthritis of latent rheumatic fever activated by scarlatinal streptococci. Among 5,549 patients with scarlet fever seen by one physician[63] were ninety-nine cases of true scarlatinal arthritis (types 1 and 2), an incidence of 1·8 per cent. The effect of sulphanilamide in preventing or curing such arthritic conditions is being studied.

Rheumatic Fever

Clinical Data.—Rheumatic carditis affected the school children on two northern American Indian reservations nine times as often as those on a southern reservation;[64] the hospital incidence of rheumatic carditis in Chicago was more than four times as great as that in the southern city of Galveston.[65] These are further evidences of the greater predilection for the disease in the northern States. A study of 112 rheumatic families led to the conclusion that an hereditary factor, transmitted as a single autosomal recessive gene, is distributed among the population, which makes the bearer susceptible to rheumatic fever,[66] but hereditary susceptibility may not be the sole requirement for its development. The symptomatology of several hundred new cases of rheumatic fever was analysed.[4] Among a population of about 130,000,000 there are more than 1,000,000 Americans with rheumatic carditis, and 40,000 deaths therefrom each year, the average age at death being thirty years.[67] Some believe that adult heart valves practically never possess bloodvessels; when seen they are the result, not the predisposing factor, of antecedent rheumatic inflammation.[68] Others believe that most normal heart valves possess bloodvessels, but their incidence in a given valve does not correspond to the incidence of rheumatic valvulitis in that valve, since active or healed valvulitis can be found in the absence of bloodvessels.[69] By injecting 2 to 3 c.c. of the rheumatic patient's own blood into the region of the olecranon, subcutaneous nodules were produced in 45 per cent. of eighty-two rheumatic patients; in only one of thirty-four

non-rheumatic persons.[70] The histologic characteristics of these induced nodules were essentially similar to those of spontaneous type. According to one writer,[71] there is no sound evidence that erythema nodosum is related to rheumatic fever. Another physician,[72] after studying 143 cases of erythema nodosum, regarded rheumatic fever merely as one of several provocatives of erythema nodosum, a non-specific skin reaction to various toxins.

Laboratory Data.—The value of lead IV electrocardiograms in rheumatic fever is in dispute; some[73] consider them superior to, others[74] regard them as of no more value than, orthodox leads in giving evidence of rheumatic carditis.

Ætiology.—No new hypotheses or important variants of old hypotheses have been elaborated. The relationship of streptococcal pharyngitis to rheumatic fever remains obscure; studies made in New York City indicated a close connection between the two;[75] others made in Galveston, Texas, did not.[65] Although the skin of rheumatic patients is hypersensitive to streptococci, especially to hæmolytic streptococci, this is no proof that hæmolytic streptococci are of ætiological importance; one worker[76] found that the positivity of skin tests was directly proportional to the content of non-specific irritant substances. Many patients with rheumatic fever possess anti-C precipitins (antibodies against the C, or carbohydrate, fraction of hæmolytic streptococci), but so do some normals and some patients with other articular diseases; such precipitins are not specific for rheumatic fever and must be interpreted with caution.[77]

The argument suggesting a relationship between rheumatic fever and deficiency of vitamin C has been restated,[78] but not especially strengthened, by newer work. Obviously the cause of the disease remains unknown. Many still believe that rheumatic fever is closely related to beta (but not to alpha or gamma) hæmolytic streptococci, and the fact has been stressed that the naso-pharyngeal infections which precipitate rheumatic fever are mostly due to group A (Lancefield) hæmolytic streptococci. But if this is so, why is sulphanilamide, which is so effective against many such streptococci, so ineffective in rheumatic fever? To some this forms a strong argument against a direct relationship between rheumatic fever and hæmolytic streptococci.

Treatment.—Unfortunately very little, if any, progress has been made in this direction, and prolonged rest remains almost

the alpha and omega of therapy. Preliminary studies have indicated that sulphanilamide is of no value; indeed, it seems to be particularly toxic to patients with rheumatic fever.[4] "The toxic action of sulphanilamide in active rheumatic fever so far outweighs the beneficial therapeutic effect that its administration to patients with this disease does not seem justified."[79] Tonsillectomy is still practised as a measure of possible value. Vaccines have proved of little worth. Some[20] expressed the belief that fever therapy is of value. No distinct benefit has been noted from the use of vitamin C. Perhaps too much has been expected of it;[78] if vitamin C deficiency prepares the soil for an infection to produce rheumatism, the vitamin deficiency is only contributory and its correction cannot materially affect valvular and other damage.

Sydenham's Chorea

Chorea has been regarded as (1) a symptom of rheumatic fever; (2) a symptom of several diseases, including rheumatic fever; (3) an independent disease which may accompany rheumatic fever. The first view was supported by three recent reports[4] which stressed the frequency with which carditis ultimately develops in cases of chorea. The third view was upheld in a report which concerned 137 choreic patients, about half of whom never developed any other signs of rheumatic infection, such as abnormal sedimentation rates or blood counts, carditis or arthritis.[80] Induced fever continues to be the method of choice in treatment. Several physicians[4] reported prompt cure of about 80 per cent. or more of patients so treated, marked improvement of others. Remissions were rare and complicating carditis seemed to be benefited. However, two choreic children without carditis developed fatal, uncontrollable fever, induced in one case by injection of typhoid vaccine, in another case by artificial fever therapy.[81, 82]

Rheumatoid (Atrophic) Arthritis

Clinical Data.—Most American physicians feel unable to make a sharp distinction between rheumatoid arthritis and infectious (infective) arthritis. They regard the latter as synonymous with, or at most a clinical variety of, the former. Criteria for the identification of rheumatoid arthritis were suggested as follows:[83] (1) Data considered essential—fusiform fingers and

polyarticular involvement; (2) helpful data, often but not always present—presence of agglutinins for hæmolytic streptococci and the " characteristic " pathologic reactions in synovial tissue and subcutaneous nodules; (3) non-essential data frequently present—vasomotor disturbances, muscle and skin atrophy, presence of antistreptolysins and precipitins, rapid sedimentation rate, " characteristic " roentgenographic changes.

Further observations on the inactivating effect of spontaneous jaundice on rheumatoid arthritis and on primary fibrositis were reported and attempts were made (so far largely unsuccessful) to reproduce the phenomenon by various means, such as use of bile salts, transfusions of jaundiced blood or artificial hyperbilirubinæmia.[84, 85] The strangely beneficial effect of jaundice may be more basic than simply an antirheumatic phenomenon. When one patient developed cinchophen jaundice a " momentous thing " occurred: the patient was promptly relieved not only of his chronic rheumatic symptoms, for which the cinchophen had been taken, but also of symptoms of severe hay fever. The " anti-allergic " effect apparently continued, so that the next year during hay-fever season the patient was able literally to romp in ragweed.[86]

Laboratory Data.—The relative value of laboratory data in diagnosis and in estimating activity and prognosis was studied. Sedimentation rates were the most useful; Arneth-Schilling counts of filamented and non-filamented leucocytes were valuable; the Vernes resorcinol test on serum was less useful.[87] Results of glucose tolerance tests may sometimes be abnormal in rheumatoid arthritis and in other chronic diseases because of (1) a disturbance of pancreatic function, (2) circulatory disturbances accompanied by removal of sugar from the blood, (3) hepatic dysfunction, the effect of toxæmia on the liver, not on the pancreas. In one series of cases[88] hepatic dysfunction, as indicated by excretion of azorubin S, affected 55 per cent. of 100 patients with rheumatoid arthritis.

Ætiology.—No significant progress on the problem of ætiology was reported. In recent studies serum agglutinins to hæmolytic streptococci have been found in a lower percentage (only 24 to 53 per cent.) of cases than previously was noted. The significance of these agglutinins is still debated.[4, 87] Antifibrinolysins usually are normal, but may be increased in early and acute cases; perhaps the disease is initiated, but not kept up, by hæmolytic strepto-

cocci.[89] From current data one cannot certainly conclude that streptococci cause the disease. No new data of significance were reported in favour of the hypothesis of bacterial allergy, of vitamin deficiency, or of "altered metabolism."

TREATMENT.—Those American physicians who are optimistic about the results of removing foci of infection are still a shade more numerous, or at least more vocal, than the pessimists. The principle of removal of foci usually is "radicalism within the limits of common sense." Vaccines are definitely waning in favour, but many feel justified in using them as non-specific adjuvants; such therapy is being continued, however, in the face of strong criticism.[90] The empiric use of chaulmoogra oil, given by intramuscular injection, seemed helpful to one physician:[91] focal and general reactions, sometimes sterile abscesses, were noted; perhaps the effect is similar to that from non-specific proteins. The evidence suggesting that a primary vitamin deficiency is present or that an excess intake of vitamins B, C, or D is definitely helpful is not striking. Some are still strongly advocating massive doses of vitamin D, but others are abandoning this therapy as useless and sometimes dangerous, and the Council on Pharmacy and Chemistry of the American Medical Association found no scientific evidence to support the claims made for it.[4] Causalin (causyth) likewise has been condemned as "unsafe and dangerous," and claims made for "subenon" have been called "ridiculously optimistic."[4] Several physicians are still reporting good results from injections of colloidal sulphur, but there seem to be few new converts to this form of treatment, and, as far as I know, it is not being used at any of the larger, more established clinics for rheumatic diseases.

Aware of the number and too frequent severity of toxic reactions to gold, American physicians have been hesitant about using it in spite of the growing favour with which it is regarded in England and on the continent of Europe. Now it would appear that the dangers of chrysotherapy have been considerably lessened by rather sharp reductions in the individual and total doses used. Hence, physicians in several American clinics are studying its effects. Preliminary results in the treatment of one series of twenty-two patients were marked improvement of 54 per cent. with notable reductions in sedimentation rates.[92] There is a tendency in the United States to give equal doses, not higher than 50 or 100 mg. of gold, perhaps twice a week.

Preliminary results with sulphanilamide have been distinctly disappointing and serious toxic reactions occasionally have been noted.[4]

Although there are more than 8,000 mineral springs in the United States, there are only twenty or thirty American spas and only four or five of them are really well known. Although almost every community has the services of ill-trained manipulators and adjusters, the supply of medically trained physical therapists is entirely inadequate. Therefore, physicians and physical therapists are waging a quiet campaign to educate intelligent rheumatic patients in those simple and harmless methods of home physical therapy which are so useful and necessary as an adjunct to formal physical therapy. Short-wave therapy has its advocates, but most workers deny that it has a specific or superior mode of action. Results of fever therapy are still not impressive, although they were better in the acute and subacute cases than in chronic rheumatoid arthritis.[93]

Osteo-arthritis

In spite of the great frequency of its occurrence, this disease is a much neglected member of the rheumatism family; few indeed are the publications which have this disease as their sole or chief concern. Surely a disease so prevalent and distressing, even though it is not as serious as rheumatoid arthritis, deserves more serious consideration than to be used almost solely as control material for studies on rheumatoid arthritis. Not a single new clinical report on it appeared in the United States during the period under review. The current writings of our English colleagues have not only been meagre, but have shown little unanimity of opinion even as to the clinical and roentgenographic features of the disease.[4] Two reports[94, 95] described improved methods for making roentgenograms of knees; those made with knees in flexion give better views of intercondyloid fossæ and demonstrate early osteo-arthritic changes not visible in ordinary roentgenograms.

Ætiology.—The rôle of chronic trauma as a cause of certain types of osteo-arthritis was emphasised in one report;[96] the experimental production of patellar displacement in rabbits caused the development of osteo-arthritic changes similar to those seen in patients with patellar dislocation. According to another

report[97] interference with articular blood supply by reason of juxta-articular adiposis dolorosa may be one of the causes of osteo-arthritis of man.

TREATMENT.—Those who have so enthusiastically advocated sulphur or concentrated vitamin D generally have failed to make any distinction between rheumatoid arthritis and osteo-arthritis, and have claimed good results indiscriminately in both types. Because of this, and because many others have failed to confirm their value, these remedies are in little repute. Fever therapy has been of little value. Some still favour iontophoresis with mecholyl[98] or with histamine.[99] A "new" procedure, bone puncture or forage, used as early as 1890 by Nobel Smith, but recently revived, seemed to provide some relief in several cases of osteo-arthritis of hips.[100]

BACKACHE AND SCIATICA

Because of recent advances in knowledge of the pathologic physiology of the spinal column, the interest of physicians in cases of backache and sciatica has greatly increased. The idea that certain cases of backache and sciatica are caused by tight fascia lata and ilio-tibial bands, and that complete relief can be obtained by fasciotomy in about 75 per cent. of cases, was again expounded.[101, 102] One surgeon[102a] expressed the belief that fasciotomy is of value only as it releases pressure on the pyriformis muscle and sciatic nerve, which pressure he conceives to be the frequent cause of sacro-iliac backache and sciatica. Numerous writers expressed the opinion that in most cases pain in the neck or low in the back, or sciatica, is not due to primary arthritis of the spinal column, but is secondary to, and is rather a late manifestation of, alterations in intervertebral disks—"discogenetic disease." In some instances primary thinning of disks (not due to nuclear prolapse, but possibly the result of chronic trauma) produced narrowed intervertebral spaces and subluxation of articular facets, with resultant segmental neuritis.[103, 104] By proper technique, narrowing of the foramina can be demonstrated roentgenographically. The following were recommended: head traction and neck stretching (Hanflig method, 1936) for cervical lesions, reduction of lumbo-sacral lordosis by plaster jackets, postural exercises, braces or lumbo-sacral fusion for lesions low in the back.

From two clinics in particular came a series of papers on the syndromes produced by posterior prolapse of intervertebral disks and of nuclei pulposi,[105-110] the roentgenographic demonstration of filling defects at the site of ruptured disks, and the surgical correction of the lesions. Space does not permit a review of the details of these reports; they were summarised in the *Fifth Rheumatism Review*.[4] Criteria for a diagnosis of ruptured disks have been established with considerable accuracy and laminectomy should not be performed unless most of the requirements have been met. Prompt and complete relief resulted from laminectomy and removal of protruded disk material in thirty-three of fifty cases[109] and in thirty-two of fifty-eight cases;[106] one post-operative death occurred among these 108 patients.

Symptoms similar to those from protruded disks (chronic low back pain generally with sciatica, sometimes numbness of leg or buttock, muscle atrophy or weakness, altered Achilles reflexes) and filling defects in roentgenograms made after injections of lipiodol similar to the defects seen in association with protruded disks also can be produced by hypertrophy of ligamenta flava, according to some.[111] Relief was obtained by removing involved laminæ and ligaments.

Spondylitis

Ankylosing Spondylitis.—Newer roentgenologic methods were described[112] for visualising facets and foramina, and it was stated that thereby involvement of lower thoracic apophyseal and costo-transversal joints sometimes can be demonstrated in spondylitis ankylopoietica several years before sacro-iliac involvement.

Spondylitis Osteo-arthritica.—The present view is that this is not a true form of arthritis, but a form of spondylosis, an exostotic reaction to mechanical irritation arising as a result of degenerative changes in intervertebral disks and vertebral bodies. Contrary to the opinion of many, some now[113] believe it is *not* a common cause of low back pain *with* sciatica. The clinical features in 294 cases of "hypertrophic spondylitis" were reviewed: symptoms affected 99 males and 195 females.[114] In addition to the usual methods of treatment, gentle traction was advised.[112, 114]

Gout and Gouty Arthritis

Clinical Data.—Efforts to familiarise physicians with the clinical characteristics of American gout are being successfully carried out and recognition of gout is becoming distinctly more frequent in the United States. However, many cases are still misdiagnosed because of the mistaken notion that the disease is almost non-existent, or at least rare. The classical pattern of gouty arthritis is generally accepted as being one of recurrent attacks with complete symptomatic remissions; later, in some cases chronic gouty arthritis develops.[115-117] American students of the disease cannot agree with the view expressed by many of their English colleagues that gouty arthritis, especially among women, may appear insidiously, progress slowly without complete remissions, and be chronic from its inception. The tendency for acute attacks to be seasonal in appearance, and often consistently related to certain provocations, was well illustrated in one current series of cases.[116] The criteria which I use in making the diagnosis of gout and gouty arthritis were restated by my colleagues.[116] Recently I visited various American physicians interested in gout and summarised their views on the diagnosis and management of the disease.[115]

Ætiology.—Some cannot regard gout as truly a disturbance of purine metabolism, since in gout there is no abnormality of intermediary purine metabolism, although there is an obvious disturbance in the disposition of uric acid. Some consider gout due to a peculiar selective renal insufficiency; others consider it due, not to a primary renal disturbance, but to a functional disturbance of the vegetative nervous system, involving renal innervation.[118] Among the clinical phenomena correlated with this latter hypothesis were the beneficial effects of cinchophen and the sometimes malevolent effects of ergotamine tartrate (gynergen) on patients with gout.

Treatment.—Too often patients are treated for their gout only during an acute attack; the importance of interval treatment as a prophylactic against chronic gouty arthritis and against the possibly fatal late lesions of gout in kidneys and bloodvessels should be more widely appreciated. In spite of its occasional toxicity, cinchophen is still being used by many physicians of wide experience with gout, not only during attacks, but also intermittently between attacks for long periods.[4] Others con-

demn the use of cinchophen under any circumstances, and believe that there is no "safe method" of giving it even if "given cautiously under observation."[119] It should be noted, however, that no case of gout has been listed among the few cases of cinchophen toxicity reported in recent years. For those patients who fear, or do not well tolerate, cinchophen the combination of sodium salicylate (60 grains) with amino-acetic acid (glycine) (150 grains) daily during attacks and intermittently thereafter has been used with apparently some success as a substitute for cinchophen.[115, 116] (In the Fourth Report of this series note was made that Jennings had revived interest in the use of salicylates alone as a substitute for cinchophen.) If it can be shown that salicylates, with or without amino-acetic acid, and with proper dietary control, will effectively control gout, it would be senseless to support the cause of cinchophen longer. Some of us believe that many patients cannot control their gout by diet alone; that many patients can tolerate cinchophen intermittently more readily than the larger doses of salicylates required; and that, in spite of our inadequate knowledge of gout, an attempt to control the hyperuricæmia of gout is sound therapy even though hyperuricæmia may be a secondary, not a primary factor in the disease.

Psoriatic Arthritis

Cases of psoriatic arthritis are too infrequently recognised; dermatologists tend to ignore the joints; internists ignore the skin; consequently, the possible relationships between the two are not disclosed. Those who accept this entity agree that its diagnosis depends mainly on the close relationship which exacerbations and remissions in skin may bear to those in joints, and on noting the beneficial effects on the joints which not infrequently occur when skin lesions are treated vigorously. Aside from these and a few other rather distinctive features (frequent involvement of terminal phalangeal joints of fingers and toes with associated psoriasis of contiguous nails; sometimes unusual roentgenographic changes in *late* psoriatic arthritis), this form of arthritis resembles rheumatoid arthritis in many respects. New cases of true psoriatic arthritis (not merely cases of psoriasis incidentally associated with any rheumatism) were described; the application of Goeckerman's (1931) regimen (ultra-violet irradiation and coal-

tar ointment) resulted in distinct benefit for skin and joints.[120, 121] Of fifteen patients with psoriasis (joints not mentioned) given 300,000 to 400,000 units of concentrated vitamin D for several weeks, the skin of eleven cleared completely.[122]

Allergic, Metabolic and Endocrine Arthritis

Little appeared to clarify these terms. A number of writers manifested their receptivity to the idea that offending food or bacterial antigens can produce allergic arthritis in susceptible persons. They may be right, but the data given with their reports of cases of the supposed conditions are meagre, incomplete and not convincing. Incapable of accurate definition, the term "metabolic arthritis" is disappearing from American literature; it should not be revived until new discoveries have been made by which the term can be better defined. The terms "endocrine, climacteric and menopause arthritis" also seriously need examination and overhauling, or else they, too, should be discarded. Among the proponents of the entity last mentioned, there is no unanimity of opinion as to whether it is synonymous with osteo-arthritis, whether it is rheumatoid arthritis occurring at the menopause, or whether it is a separate disease. Although writers speak rather glibly of its supposed pathologic characteristics (villous synovitis with degenerative arthritis), no one in recent years, or ever perhaps, has presented any photomicrographic evidence of its supposed characteristic pathologic changes.

Intermittent Hydrarthrosis

In 1929 Weisman-Netter proposed the use of ergotamine tartrate (gynergen) for intermittent hydrarthrosis; by this method the disease apparently was stopped in one recent case.[123]

Fibrositis

This term is still on probation in the United States. Diagnoses of fibrositis are made and defended by only a few American physicians. One physician noted 262 cases of fibrositis among 900 patients referred to an arthritis clinic.[124] Still disturbing to American physicians is the almost complete lack of accurate knowledge of the supposed pathologic changes in the disease and the tendency for numerous physicians who write familiarly

of it to copy rather than to defend and, more important, to extend vigorously Stockman's pioneer work on the pathology of fibrositis. Some of the leading American rheumatologists doubt the existence of the so-called fibrous nodules and, believing that the term " fibrositis " is too often used as a catch-all, refuse to accept the entity. In part one cannot blame them, because certain physicians are likely to perpetuate confusion by adulterating the syndrome of fibrositis with an array of " algias."

The usual methods of treatment are being tried. Apparently unable to improve them, American physicians are still following the precepts of their English colleagues, and, among other things, some of us are, with more hope than faith, still trying to " rub the nodules away." Admitting that he was able to relieve some patients by physical methods and bymassage of nodules, one physician commented: " One is still led to wonder whether these nodules are as important as many writers believe and whether they can be rubbed away as consistently as some state."[125]

Campaign against Rheumatism

To be fully successful a campaign against rheumatism needs occasional dramatisation, special occasions when both the medical profession and the public are informed as to the seriousness of the problem and the amount of physical suffering and economic waste it engenders. But for the ultimate success of such a campaign a sustained, undramatic, slowly progressing growth of interest in the rheumatic diseases among physicians and laymen is much more important than isolated, sporadic days of high resolve. It is along these latter lines that the campaign is being waged in the United States. The American Rheumatism Association now has about 250 members. This association and its parent body, the American Committee for the Control of Rheumatism, have the important and cordial support of the American Medical Association, which has opened its programmes to an increasing number of reports on the problem of rheumatism. The American Rheumatism Association has created associate memberships for interested laymen, social workers, insurance executives and members of professions allied to medicine; to them are sent bulletins summarising information of current interest. The association's conferences on rheumatic diseases, held annually at the time of the meetings of the American Medical Association,

are increasingly well attended.* New clinical clubs and small groups of physicians are meeting in many of the larger cities for the purpose of special group study of these diseases. New research grants have been made for the establishment of " arthritis units " in several university and city hospitals—for example, at Harvard University, at the University of Michigan and at Welfare Island, New York City. One new large philanthropic foundation is giving a proportion of its funds to individual clinical investigators to aid them in their researches on various phases of the rheumatism problem. In the Commonwealth of Massachusetts, which is perhaps the most progressive in the matter of social legislation as far as the problem of rheumatism is concerned, an Act recently was passed providing for the hospitalisation of a certain number of patients and their treatment for periods as long as six months.

Throughout the world medical science has notably increased the span of man's life, but there is danger that too great a fraction of that lengthened span may be made miserable by the painful symptoms of degenerative arthritis, if not by some more serious articular disability. It is now truly medicine's duty, having added to the quantity of human life, to add also to its quality. Whatever successes are gained by such campaigns against rheumatism will go a long way toward fulfilling that obligation.

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* In the spring of 1940, just prior to the annual meeting of the American Medical Association (to be held in New York City), the American Rheumatism Association will hold its annual conference on rheumatic diseases in connection with the bi-annual meeting of the Ligue Internationale contre le Rhumatisme. Plans are already under way to provide suitable settings for these meetings, and we are looking forward with great pleasure to the opportunity of playing host to our distinguished colleagues from overseas. Tentative plans call for one week of medical and social assemblies in New York City, Philadelphia and Boston. It is to be hoped that the opportunity to attend the sessions of the Ligue, the American Rheumatism Association's conference and the scientific sessions and exhibits of the American Medical Association, as well as to sample the diversions of these American cities, made the more unusual by the presence of the 1940 New York Fair, will appeal to a large number of our colleagues from abroad.

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PRELIMINARY OBSERVATIONS ON THE OXYGEN AND CARBON DIOXIDE GAS TENSIONS IN THE KNEE-JOINT IN NORMAL AND PATHOLOGICAL CONDITIONS

By OSWALD A. SAVAGE,

AND

H. J. TAYLOR,

The injection method of estimating the carbon dioxide and oxygen tissue gas tensions has been extensively used for observations in the pleural cavity, the peritoneal cavity, the bladder, the washed-out stomach and intestine, the subcutaneous tissues and the body fluids. The principle of the method is that air, nitrogen or a mixture of oxygen, carbon dioxide and nitrogen is injected into the tissue or part whose oxygen and carbon dioxide tension it is desired to measure. The gas is left until in equilibrium with the tissue gases and a sample is then removed and analysed. The subject has been reviewed by J. Argyll Campbell (1931). It cannot be said that the presence of the injected gas is usually normal, but injection of gas into the pleural cavity is a routine method of treating tuberculosis of the lung and the injection of oxygen into the sheath of the nerve is a method of treating sciatica. We can find no data with regard to gas tensions in joints. It is from this point of view that we have made measurements of gas tensions in joints, both normal and diseased.

Previously gas has been injected into joints with two objects in view:

(*a*) For Diagnostic Purposes.—Inflation of the joint, it is claimed, gives clearer radiographs and thus facilitates examination. It has been used by many authors, notably Terracol and Colaneri (1920), Prat (1920), Kleinberg (1921), Kasin (1922), Balensweig (1924), Cattaneo (1923), Bernstein and Arens (1926), Werndorff (1929), Ulrichs (1930), Bircher (1931), Purves and Bilcliffe (1924), Oberhalzer (1933-34), Junghagen (1933), Schrum (1933), Bircher and Oberhalzer (1934), Simon, Hamilton and

Farrington (1936), Bohlman (1936), Lachowsky and Goldman (1936), Forgandes (1937), Scheckel (1937), and Quaintance (1938).

(*b*) For Therapeutic Purposes.—The inflation of a joint has been used by many workers as a therapeutic measure. The injected gas might be expected to exert a cushioning effect. Fluid in a joint exerts a hydraulic action with the slightest movement, and this tends to stretch the joint capsule. Gas, being compressible, will prevent this; it will also tend to separate inflamed parts, and thus prevent adhesions. Injection of oxygen into a joint also tends to inhibit the growth of bacteria, such as gonococcus, which require a low oxygen tension for growth. The injection of gas with this object in view has been widely used, notably by Rost (1920-21), Raymond (1923), Purves and Bilcliffe (1924), Caccia (1927), Reich (1927), Rechtman (1929), Porter and Rucker (1929), Henson (1930, 1936), Mondor (1931), Vilar (1931), and Vohlman (1936).

Technique of Gas Injection

The knee-joint was the only one used in this work. The prepared knee was flexed at 45° and the site of entry of the needle infiltrated down to the capsule with ½ per cent. of procaine hydrochloride solution. The best site was found to be in the recess between the lower and outer edge of the patella and the lateral condyle of the tibia. The gas was injected through a Clive Rivière No. 1 needle attached to a Heaf's pneumothorax apparatus. The chamber of the latter was filled from a cylinder, the needle inserted into position, and gentle pressure applied by hand to the top of the chamber. Before commencing to inject the gas a pressure reading was taken on the manometer of the apparatus, and on no occasion was there found to be either a positive or a negative pressure inside the joint which could be recorded on a scale reading to 1·0 cm. of water, nor was any such pressure obtained with small movements of the joint. It was usually found that before any appreciable amount of gas could be forced into the joint the pressure had to be raised to above 25 cm. of water. Gas could then often be heard bubbling into the joint. Injection may be carried to the point at which discomfort begins to be felt. The joint is then distended with gas, and it was usually found that about 300 c.c. could be injected

without causing undue pain. The first few times this technique was carried out the presence of gas was confirmed radiologically (see Fig. 1), but as it was always obviously present on palpation this was dispensed with as giving no further information. Gas could usually be felt in the joint for at least four days. Difficulty was experienced with cases of osteo-arthritis. Little gas could be injected into these joints, making the taking of subsequent

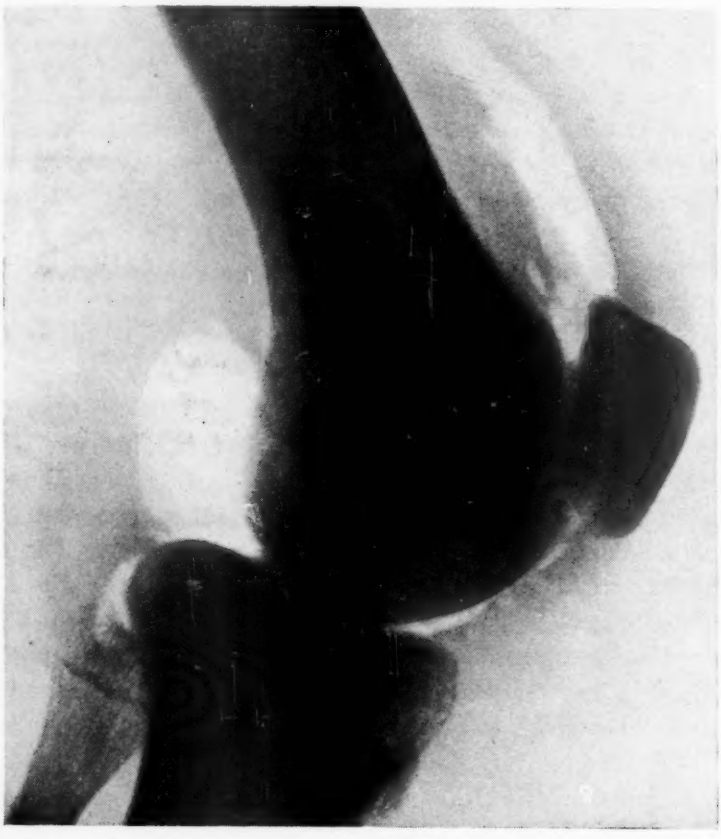

FIG. 1.—X-RAY PHOTOGRAPH OF KNEE-JOINT AFTER GAS HAS BEEN INJECTED.

samples for analysis most difficult; in fact, it was only possible to obtain a sample of gas for this purpose from one out of six cases. Gas for analysis was obtained in a syringe filled with lightly acidified 80 per cent. glycerine. The needle of this syringe was inserted into the joint at the site used for the injection of the gas after local anæsthesia as before. The capsule was compressed by hand and the gas bubbled out into the syringe.

The gas sample was analysed by the method described by Campbell and Taylor (1935). A note is taken of the barometric pressure, since this is necessary in calculating the gas tensions. No patient complained of discomfort either during or after gas injection.

Results

No data are available on the normal gas tensions in the knee-joint, and it was therefore necessary for this purpose to carry out some determinations on normal joints.

Case 1.—Man, aged twenty-four. Right knee external semilunar cartilage removed, right knee injected. Gas tensions: CO_2, 31 mm. Hg; O_2, 33 mm. Hg.

Case 2.—Man, aged thirty-one. Gas tensions: CO_2, 29 mm. Hg; O_2, 34 mm. Hg. These two results are in good agreement, but before these figures are accepted as the correct ones we consider that further experiments are desirable.

Case 3.—In a case of traumatic effusion into the knee-joint which had subsequently cleared up it was found that the gas tensions were: CO_2, 40 mm. Hg; and O_2, 16 mm. Hg. This oxygen tension was much lower than that in the normal joints 1 and 2, and it is obvious that the case cannot be taken as a normal, although recovery appeared to be complete.

Pathological Conditions

Case 4.—Rheumatoid arthritis: Acute rheumatoid arthritis. Male, aged eighteen. Duration one month; marked swelling of the peripheral joints; fever 99° to 102° F.; a typical example of rheumatoid arthritis. Gas injected into the left knee. (*a*) Arthrotomy and lavage performed three days later, and the joints seen to be full of glairy mucoid material which was squeezed out. Synovial membrane hyperæmic. One month later right knee injected with gas (*b*); ten days later this was repeated (*c*). Gas tensions: (*a*) CO_2, 18·2 mm. Hg; O_2, 56 mm. Hg. (*b*) CO_2, 15 mm. Hg; O_2, 62 mm. Hg. (*c*) CO_2, 19 mm. Hg; O_2, 52 mm. Hg.

Case 5.—Acute rheumatoid arthritis. Male, aged nineteen. Duration three months; increasing swelling of hands, feet and knees; fever to 101° F.; marked muscle wasting. Gas injected into the left knee. Gas tensions: CO_2, 20 mm. Hg; O_2, 55 mm. Hg.

Case 6.—Rheumatoid arthritis subacute. Male, aged fifty-nine. History of increasing pain and stiffness in hands, wrists and knees for a year. Effusion into both knee-joints; swollen interphalangeal joints. Considerable wasting of interossei and quadriceps muscles. Slight loss of weight. The condition was still active clinically and the sedimentation rate was 62 mm. Westergren after 1 hour. Both knee-joints injected with gas. Gas tensions: Left knee: CO_2, 48 mm. Hg; O_2, 20 mm. Hg. Right knee: CO_2, 50 mm. Hg; O_2, 15 mm. Hg.

Case 7.—Rheumatoid arthritis subacute. Male, aged forty-five. For seven months increasing stiffness and swelling of hands and feet. Loss of weight and malaise. Muscle wasting marked. Sedimentation

rate, 22. Right knee injected. Gas tensions: CO_2, 45 mm. Hg; O_2, 12 mm. Hg.

CASE 8.—Rheumatoid arthritis subacute. Male, aged twenty-eight. History of increasing stiffness and swelling of hands and feet for three months. Loss of weight. Fever 100° F. occasionally. Muscle wasting evident. Sedimentation rate, 57 first hour. Gas tensions: CO_2, 38 mm. Hg; O_2, 30 mm. Hg.

CASE 9.—Gonococcal arthritis. Male, aged twenty-five. Gonorrhœa five years before. Painful and swollen right knee for four weeks. Gonococcal fixation test positive in blood. Prostatic bead nil. Right knee injected. Gas tensions: CO_2, 45 mm. Hg; O_2, 9 mm. Hg.

CASE 10.—Male, aged twenty-nine. Four months pain and effusion both knees. The patient denied gonorrhœa and the joint fluid gave negative gonococcal fixation tests. The condition was thought to be gonococcal arthritis clinically and an attack of epididymitis occurred while in hospital. After three bouts of artificial fever the condition cleared up. Left knee injected. Gas tensions: CO_2, 30 mm. Hg; O_2, 20 mm. Hg.

CASE 11.—Osteo-arthritis. Female, aged sixty-three. Five years pain and swollen knees. Weight 15 stone. B.P. 210/120. Sedimentation rate, 2. Crepitus and limitation of movement of both knees. X-rays show irregularity of joint surfaces and osteophytic outgrowths in both knees. Gas tensions: CO_2, 46 mm. Hg; O_2, 7 mm. Hg.

CASE 12.—Male, aged forty-four. Twenty years backache. Marked kyphosis with spinal rigidity. X-rays show calcification of spinal ligaments and obliteration of the sacro-iliac joints. Gas injected into the left knee and samples removed after twenty-four and forty-eight hours. Gas tensions (twenty-four hours): CO_2, 46 mm. Hg; O_2, 12 mm. Hg. Forty-eight hours: CO_2, 42 mm. Hg; O_2, 15 mm. Hg.

These results are summarised in table below.

Diagnosis.	*Gas Tensions.*	
	O_2.	CO_2.
Rheumatoid arthritis acute	56	18·2
	62	15
	52	19
Rheumatoid arthritis acute	52	20
Rheumatoid arthritis subacute	20	40
	15	50
Rheumatoid arthritis subacute	12	45
Rheumatoid arthritis subacute	30	38
Gonococcal arthritis	9	45
Osteo-arthritis	7	46
Spondylitis ankylopoietica	15	42
Traumatic effusion	16	40
"Normal"	33	31
"Normal"	34	29

CONCLUSIONS

The small number of cases reported precludes the drawing of any definite conclusions, but it seems significant to us that in acute rheumatoid arthritis the O_2 tension is higher and the CO_2

tension lower than normal, as might be expected in an inflammatory condition. We would suggest that the values for the later stages of this disease and in conditions of osteo-arthritis, gonococcal arthritis, spondylitis ankylopoietica, and in traumatic effusion (after the effusion has cleared) suggest some permanent interference with the blood and/or lymph supply to the joint in these cases, as has been shown histologically by Timbrell Fisher. Further work is in progress on this subject.

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ABSTRACTS FROM CURRENT LITERATURE

POLYARTHRITIS IN RATS. W. A. Collier (Eijkman Instituut, Batavia). *Geneeskundig Tijdschrift voor Nederlandsche-Indie.* Afl. 45, Deel 78, 1938.

IN the course of certain researches among Norwegian rats one animal was met with in which both hind feet were swollen. Material from the affected tissues was injected into four white rats, chosen because of the close relationship of the white rat to the Norwegian strain, and the same symptoms due to a polyarthritis were reproduced. Tissue from an affected joint suitably prepared with aseptic precautions was injected into the plantar region of experimental animals. This produced a slight inflammation at the point of injection which quickly passed off. After an incubation period of usually five to seven days, rarely eight days, the leg began to swell near the tibio-tarsal joint, and sometimes also in the vicinity of the metatarsal joints, and this rapidly increased and in many cases spread to the corresponding joints of the other hind leg, the legs swelling to two or three times the normal size; in a few cases, however, the process remained localised and gradually regressed to normal. Some fluid was found in the joints which was culturally sterile unless secondarily infected; rarely suppuration was observed.

In some animals the arthritis spread to the front legs, and rarely to the end joints of the tail. Some of the animals died, but the others made a slow recovery with subsidence of the swelling.

In many cases a little fluid was found in the pericardium, and a thin pleural exudate poor in cells; very seldom there was also a peritoneal exudate, but in none of these fluids were any bacteria discovered microscopically.

The histological findings were inconclusive and not sufficiently extensive, and need to be repeated; radiological examination showed changes in the joints and adjacent bony tissues.

In further investigations 186 rats were injected subcutaneously in the plantar surface, of which 181 became ill; in fifteen others the infected material was rubbed into scarifications on the legs and

all were infected; eight were injected subcutaneously in the abdominal wall and five were infected; nine were injected intraperitoneally and four became definitely ill. In the latter cases the formation of pericardial and pleural exudates was specially marked, but the local polyarthritic symptoms were as severe as in the others.

TABLE I.

Method of Infection.	*Number of Infected Animals.*	*Positive Results.*	*Negative Results.*
In the plantar region	186	181	5
Scarification	15	15	—
Subcutaneously	8	5	3
Intraperitoneally	9	4	5

Experiments were carried on to determine if the disease might be communicated by contact, but normal rats placed in the same cage with infected ones were unaffected, nor did they develop immunity; this was also the case when the normal rats were scarified on both hind legs. Observations on the possibility of a prenatal infection were inconclusive.

Experiments were then made with the field rat, which is more distantly related to the Norwegian rat, and it was found to be less susceptible, as shown by a longer incubation period as well as less severe symptoms. Other rodents were less susceptible.

A further series of experiments by W. A. Collier and H. Esseveld were carried out and reported (*Geneeskundig Tijdschrift voor Nederlandsch-Indie*, Afl. 47, Deel 78, 1938).

The infecting material was obtained by amputating one of the swollen joints, rinsing it with alcohol and then with sterile physiological saline, and finally grinding it in a mortar. The substance obtained was filtered through gauze and injected into healthy animals. The following results were obtained:

Rat 219*c* was infected in the plantar region on April 2, 1938; nine days later both hind legs showed severe swelling, and the front legs were also affected, though less severely. Cultures were made on ascites agar, Löffler serum, and blood agar from the heart blood, the pleural fluid, liver, testis, brain, and joint fluid

from the left hind and the front leg. Duplicate cultures were made and half treated aerobically, half anaerobically, and checked after twenty-four, forty-eight and seventy-two hours. All remained sterile with the exception of an aerobic culture from heart blood, which showed a colony of a green streptococcus.

Three other rats were infected with the material from the first; one with blood and brain remained healthy, but the others treated with pleural fluid, liver, testis, and joint fluid all developed polyarthritis. (It is not clear whether the injections were made with mixtures of the substances referred to.—EDITOR.) Another rat was injected with the streptococci from the contaminated culture referred to above, but with negative result.

Rat 201*a* injected in the plantar region with the same result; other rats infected with material from the organs in the same way as in the previous instance; the disease developed in the cases treated from the joints and the blood, but not from the liver or pleural fluid.

Three other rats were infected in the same way and with similar results, and the secondary infections carried out in the same way with some positive and some negative results.

Cultures were made on Löffler plates on account of the work of Fischl, who cultivated corynebacilli from cases of infective arthritis in mice. Levaditi isolated a cocco-bacillus from cases of the same disease, but this also was not found in the present research. The only contaminating organisms met with were "green" streptococci, in one instance from the heart blood and in another from a joint.

These streptococci cannot be held responsible for the arthritis. Out of a total of seventy-nine aerobic and twenty-one anaerobic cultures they were found only in these two instances. In sufferers from many diseases streptococci have been cultivated. Libman pointed out that streptococci are the most important aerobic micro-organisms, acting secondarily, and therefore to be taken into account. The observations of Epstein and Kugel are also quoted; they found streptococci of various strains in a large series: in 40 per cent. from apparently normal heart valves, in 47 per cent. from the heart muscle, in 67 per cent. from the bone marrow, and in 79 per cent. from the blood.

As a further test twenty-four-hour cultures of the green streptococci referred to were injected into the plantar region of rats without any symptoms resulting.

During previous bacteriological researches on rats other micro-organisms were isolated in a few instances—Gram-negative cocci, staphylococci, thick non-motile Gram-positive rods, and a strain of staphylococcus designated B.P., which on inoculation produced localised abscesses which cleared up within a short time. Cultures of these various organisms twenty-four to twenty-eight hours old were injected into the plantar area of white rats, with the following results:

TABLE II.—INFECTION TESTS WITH STRAINS OF BACILLI FROM RATS.

Species of Bacillus.	*Origin.*	*Number of Rats Tested.*	*Results.*
Gram-negative cocci	Leg with poly-arthritis.	3	Negative.
Gram-positive thick rods ..	Ditto.	2	Negative.
Gram-positive staphylococci ..	Ditto.	3	Negative.
Gram - positive staphylococci B.P.	Spontaneously infected rat.	3	Negative.
Ditto	Ditto.	19	Abscesses, afterwards recovery.
Ditto	Ditto.	22	
Streptococcus viridans	Heart blood with poly-arthritis.	5	Negative.
Ditto	Ditto.	5	4 negative, 1 with small abscess.

From these tests it is evident that in no case did the infection of healthy rats with these organisms produce symptoms with even the slightest resemblance to polyarthritis. All the rats used in the tests were infected with material from animals with polyarthritis twenty-two to seventy-three days later, and all proved susceptible, so that no immunity had been set up.

It may therefore be presumed that the microbes found in these cultures were either present in the organs concerned or were accidental contaminations. The first is not unlikely in view of the fact that the diseases of many animals are of a very violent nature; in the affected legs as loci minoris resistentiæ secondary infections either from inside or outside may easily occur. The conclusion is therefore drawn that the cause of this rat poly-arthritis is either a very difficult or an uncultivatable carrier of bacteriological nature or an ultra-virus. Filtration tests are now

being carried out. No success has been obtained with microscopical examination even with the dark-field microscope.

The infectious arthritis of mice described by Fischl resembles the polyarthritis of rats in its early stages, but in the later stages there are differences; in mice a generalisation of the disease was never observed, in rat polyarthritis this was always the case. Fischl was always successful in cultivating the infecting organism, the *corynebacterium arthritidis muris*; in the polyarthritis of rats this was impossible. The corynebacterium is also infectious to rats and guinea-pigs, but mice proved much less susceptible to the microbe of polyarthritis than rats, and guinea-pigs are apparently insusceptible. That the two diseases are distinct thus appears certain.

Each of the organs of twelve infected white rats was used for infection of healthy rats in a further series of experiments, with the following results:

TABLE III.—INOCULATION OF WHITE RATS WITH SUBSTANCE FROM INFECTED RATS.

No.	*Interval between Original Infection and Inoculation.*	*Deformity of Animals whose Organs were used for Inoculation.*	*Results of the Inoculations with—*						
			Plantar Area.	*Blood.*	*Brain.*	*Lungs.*	*Pleural Fluid.*	*Liver.*	*Peritoneal Fluid.*
1	31 days	Both hind legs positive.		+	0	0		+	
2	40 „	All legs positive.	+	0	0		+	+	
3	45 „	Ditto	+	+			0	0	
4	45 „	Ditto	+	0					
5	47 „	Ditto	+	+	+		+	+	
6	47 „	Both hind legs positive.	+	+	0		+		+
7	47 „	Ditto	+	+		0		0	
8	48 „	Ditto	+	0	0	+		0	
9	48 „	Ditto	+	+	0	0		0	
10	48 „	One hind leg.	+	0	0	+		0	
11	48 „	Ditto	+	0	+	+		+	
12	48 „	Had been positive, later negative.	+	0	0	0		0	

SUMMARY.—So far no success has been attained in cultivating a micro-organism of ætiological importance from the affected joints in cases of rat polyarthritis. With organs bacteriologically sterile it was repeatedly possible to infect other rats. The

existence of an infective agent was proved apart from the inflamed joints in the blood, the brain, the lungs, the pleural fluid, the liver, the testis, and the peritoneal fluid.

C. W. B.

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A SEROLOGICAL TEST: THE B.B.F. REACTION FOR THE DIAGNOSIS OF ACUTE RHEUMATISM. H. Brokman, J. Brill, and J. Frendzel.

This is an important research directed to establishing a method of value in the diagnosis of acute rheumatism (Bouillaud's disease) by means of a complement-fixation reaction; it is contained in two papers.

1. *Compt. Rend. Soc. de Biol.*, Paris, 1935, vol. cxx., p. 372.—The ætiology of the disease being at present unknown, an antigen consisting of an aqueous extract of the organs of an infant dead from the malady was used, because of two possibilities:

(i) In the case of the existence of a specific pathogenic agent it would be found in the extract.

(ii) Rheumatic tissue possesses a certain specificity from the standpoint of morbid anatomy (Aschoff's nodes), and there may be a specificity analogous to that of cancerous or tuberculous tissues.

The technique of the complement-fixation reaction was used. The antigenic extract was prepared in the first instance from the liver and heart of a child dead of acute rheumatism, and employed in doses of 0·05 and 0·1 c.c. Serum specimens were examined from ten cases of clinically proved acute rheumatism (endocarditis, myocarditis, pericarditis, polyarthritis), a case of chorea, and one of a post-rheumatic affection.

The reaction was positive seven times, suspect once, and negative twice. Chorea gave a negative result. In one case of endo-myopericarditis the test was repeated three times at intervals of fifteen days, and was strongly positive each time; the conclusion is drawn that the affection was active throughout. In a case of chronic rheumatic endocarditis the serum at the first examination gave a negative result. It was only after an exacer-

bation that the examination of the serum repeated after four weeks gave a sharply positive reaction. In another case the reaction was at first positive; fifteen days later it was only feeble, the inflammatory symptoms, pericarditis and pleurisy having subsided.

To prove the specificity of the reaction two of the positive sera were submitted to the Bordet-Wassermann antigen, with negative result.

Sera from twenty-four patients suffering from diseases other than rheumatism gave a negative result in every case. Pleural fluid from a case of rheumatic pleurisy gave a positive result, while that from a tuberculous pleurisy reacted negatively.

The authors conclude that the complement-fixation reaction with their antigen may be of great practical value in differentiating the malady of Bouillaud from other rheumatic affections, and can serve as an index of the activity of the disease.

2. *Klin. Wochenschrift*, April, 1937, vol. xvi., p. 502.—In this further report by the same authors an account of more work on the antigen is given, comparison being made of extracts from the liver, spleen, and heart of three children dead of acute rheumatism, with the result that the liver extract was found to give a better result than other organs even when the heart showed Aschoff nodes. This is against possibility no. ii above.

The making of the liver antigen has now been standardised, and the procedure is described as follows: 200 grammes of liver of a child dead of acute rheumatism is minced and put into a flask with 800 c.c. of saline to which 0·5 per cent. of phenol is added as a preservative. The mixture, after shaking for four hours in an apparatus, is left for six weeks in a refrigerator at 4° C. The fluid is then decanted and filtered through paper; the filtrate is clear and used as antigen in various dilutions.

The following controls were tested: liver extract made in the same way from the liver of a case of miliary tuberculosis; liver from a case of tuberculous meningitis without tubercles in its substance; and the Wassermann antigen, alcoholic extract of heart. All gave negative results with positive reacting B.B.F. sera.

Tests.—*Children* tested *v.* B.B.F. antigen:

Normal: 51 tested, 49 negative.
Rheumatic: 69 tested, 61 positive.
Others: 60 tested, 54 negative.

Adults.—Rheumatic cases: 69 tested, 54 positive.

RESEARCHES ON THE STREPTOCOCCI—CECH: *Prague Cas. lek. ces.*, 1937, p. 583.—Experiments to clarify the ætiology of rheumatism. These experiments have shown that it is possible to sensitise rabbits with streptococcus vaccine, the best results being by the intravenous route; this sensitisation lasts about three months. By reinjection at the same point (joint) a local sensitisation may be induced. The symptoms that follow revaccination with the strepto-vaccine are of the ordinary inflammatory exudative character and altogether different from those observed in rheumatism. Cech as a result of his work cannot adopt either the views of Klinge (*Klin. Woch.*, 1930), who regards the malady as a pure reaction of hypersensitisation of the mesenchyme, or the opinion that the streptococcus is the agent of rheumatism and that allergy is the pathogenic mechanism.

CHINI AND MAGRASSI: *Policlinico*, 1935, vol. x., p. 565 (Italy).—These authors have tested the skin reaction and the agglutinating power of the serum in eighty patients against the streptococci, among them an important proportion of cases of rheumatism. The results obtained do not constitute a demonstration of the streptococcal nature of rheumatism, but are due to foci of streptococcal origin having no relation to the rheumatic process.

VACIRA: *Bull. Inst. Sier. Milan*, 1935, vol. viii., p. 737.—A study of the relation of the streptococcus to acute rheumatism, leading to the conclusion that the histological structure of the Aschoff nodes is essentially different from the structure of the focal infiltrations that are met with in rabbits experimentally infected with streptococci. The latter correspond, on the contrary, with the nodes of Graeff in man infected with streptococci with localisation in the joints. The author has not found that streptococcal strains from rheumatic patients are more particularly arthrophilic than others. The arthrophilia of the strains of streptococci is solely related to their individual degree of virulence, and does not increase with repeated passage through joints. Among animals rendered allergic by vaccination or by chronic infection, manifestations with any relation to those of rheumatism in man are never seen. The conclusion is opposed to the hypothesis that the streptococcus is the causal agent of acute rheumatic polyarthritis in man.

VIRUS INFECTION—ANDREI AND RAVENNA: *Bull. Inst. Sier. Milan*, 1935, vol. viii., p. 713.—These authors in experiments on

480 rabbits have found that by injecting young animals intraperitoneally with the blood of patients with acute rheumatism there follows after an incubation of six weeks a thrombo-endocarditis that is transmissible in series from rabbit to rabbit up to five passages. They have never isolated any germ from the cardiac lesions or the blood, and conclude that the endocarditis is transmissible by contagion from one rabbit to another and that it is due to a filterable virus. This affection has never been seen in the normal control rabbits, but it has been found in rabbits injected with blood from normal subjects and those suffering from diseases other than rheumatism. Further work is in progress.

M. H. G.

CORRESPONDENCE

The Editor of THE RHEUMATIC DISEASES.

DEAR SIR,

I am very grateful for the review of my book, "The Synovial Membrane and the Synovial Fluid," which appeared in your journal.

Deeply convinced as I am of the shortcomings of human endeavour, I sincerely appreciate criticism of my own work. Unfortunately, Dr. Bywaters made errors which cast undeserved doubt on the work of qualified investigators quoted in my book. On p. 64, line 5 from the bottom, Dr. Bywaters writes: "Miller is quoted as saying that normal human joints are under a negative pressure of 6 to 12 mm. of water. This would need a magician to prove; and unfortunately Miller is not listed in the bibliography." In my book, p. 92, line 7 from the bottom, the paragraph referred to reads as follows: "Miller has found that normal joints of living humans and dogs are under a negative pressure which amounts to about 6 to 12 centimetres of water." Dr. Bywaters mistook centimetres for millimetres. The method employed by the author quoted, far from being magical, is based on simple and generally accepted physical determination of differences in pressure. In my text, the printer's proof-reader substituted the English spelling of the name of the author as Miller. In the bibliography the name is spelled correctly: "Mueller, Walter: Biologie der Gelenke. Leipzig, Verlag von Johann Ambrosius Barth, Leipzig, 1929."

I would like to point out one other statement concerning the work of two authors besides my own which is misleading. On p. 63, line 12 from the bottom, we read, "He cites Curtis and Brunschwig that cases of osteo-arthritis show a high rate of absorption (borne out by his own case in Table III., which gave the highest phenolsulphonephthalein clearance). This is taken to mean an increased local blood supply." The authors quoted (p. 53) are not Curtis and Brunschwig, but Curtis and Brandenburg. Neither they nor myself interpreted the rate of absorption of phenolsulphonephthalein from the joints as an indication of increased blood supply. It is only pointed out that adhesions which destroy the synovial membrane decrease the rate of excretion.

You will understand that in requesting a correction of these misstatements I only act out of a feeling of obligation towards the authors whom I have quoted.

Thanking you for any courtesy,

I am, Very truly yours,

DAVID H. KLING, M.D.

EMPIRE RHEUMATISM COUNCIL

ROYAL PRESIDENT'S ADDRESS AT MANSION HOUSE

THE Lord Mayor of London presided at a meeting in aid of the Empire Rheumatism Council at the Mansion House, London, on April 25. The speakers were the Lord Mayor, H.R.H. the Duke of Gloucester, Lord Horder, F.R.C.P., Sir William Willcox, F.R.C.P., Sir Joseph Burn, Mr. Spedan Lewis, Mr. Timbrell Fisher, F.R.C.S., and Sir Walter Kinnear.

Before the meeting the following members of the Empire Rheumatism Council had the honour of being presented to the Duke of Gloucester, and the little daughter of Dr. W. S. C. Copeman and Mrs. Copeman presented a bouquet to the Lady Mayoress: Sir Joseph Burn, K.B.E., Mr. J. Spedan Lewis, Sir A. Henry McMahon, G.C.M.G. (Vice-Presidents, E.R.C.); The Earl of Iddesleigh; Sir William Willcox, K.C.I.E. (Vice-Chairman, E.R.C.); Surgeon Rear-Admiral C. V. Griffiths, D.S.O. (Admiralty Medical Services); Sir Allan Powell, C.B.E. (Mayor, Royal Borough of Kensington); Dr. C. E. Thornton (London County Council Medical Services); Lt.-General Sir George Macdonogh, G.B.E.; Mr. W. W. Grantham, K.C.; Professor L. S. P. Davidson, F.R.C.P.E. (Scottish Branch of the E.R.C.); Dr. W. S. C. Copeman, F.R.C.P. (Hon. Medical Secretary, E.R.C.); Sir Walter Kinnear, K.B.E.; Sir Robert Stanton Woods, F.R.C.P.; Mr. A. G. Timbrell Fisher, M.C., F.R.C.S.; Mr. T. W. Robinson; Mr. B. T. Clegg; Mr. C. G. Izard; Dr. C. W. Buckley, F.R.C.P.; Captain E. J. C. Chapman, M.C.; Mr. F. Dudley Hobbs.

The Lord Mayor, opening the meeting, said: "It is with great pleasure, Your Royal Highness, that I welcome the honour of your presence at the Mansion House as President of the Empire Rheumatism Council on a mission of humanity and of hope to the sufferers from Rheumatic Disease.

"The Royal House of our Empire has worked nobly to justify the oldest and the most honourable title given to Kings and Princes: that of being 'Shepherds of their People,' taking a solicitous interest in good movements for their welfare, and especially in efforts to protect them from the ravages of disease. I recall that your grandfather, King Edward, was the Captain of the army which was enrolled against the plague of tuberculosis, an army which has since made good

progress towards its objective. I trust that you, Sir, will lead this new army to war against Rheumatic Disease to a complete and speedy victory.

"I welcome also with sincere pleasure the eminent scientists and the other leaders of your Council who will constitute its General Staff, wishing you and them God-speed in the task.

"The City of London, which for some centuries enjoyed the happiness of needing no walls to protect it from the invasions of human enemies, has been always prompt to help in building up barriers against other deadly invaders, the forces of disease. It has been particularly a consistent supporter of medical research. The London School of Tropical Medicine, which has done so much to reduce the incidence of the tropical plagues, is one of the many monuments of this wise and humane effort.

"Now the call has come for a campaign against a group of diseases which has a particular domestic interest. I believe that the United Kingdom has an unfortunately high place in the list of countries where those diseases are most rife. To check their ravages is a humane effort which must claim our sympathy and support. It will bring relief from pain, and from that helplessness which is perhaps worse than pain, to very many thousands of homes."

The President's Confidence

The Duke of Gloucester said: "I am very glad to be present at today's meeting for this good cause in the City of London.

"We are living in anxious times, overshadowed by clouds which threaten the prospect of the world being allowed in peaceful security to develop so many plans for making life happier and healthier for all. It is surely proof of the sober strength of mind of the British race that, despite circumstances of no little discouragement, we can give our attention today to a campaign which aims to enlist our energies against the common enemy of human happiness—the forces of destructive disease. This shows, I think, that we are not suffering from nerves and that we are confident of a final happy outcome of present difficulties.

"The Empire Rheumatism Council, of which I have the privilege of being President, has undertaken a task of great importance: to seek out the causes of Rheumatic Disease, and therefore the means for its prevention, and at the same time to plan and to make generally available for present sufferers treatments for its cure and alleviation. Of sufferers there is a tragically great number—in the United Kingdom, at a conservative estimate, over one million adults and over 200,000 children. Many other countries are afflicted to a like degree. The American Committee for the Control of Rheumatism records that one

form of the disease, chronic arthritis, ' is generally recognised in all European and North American countries as the most important problem which that chronic disease presents. . . . A careful house-to-house survey in the State of Massachusetts has shown that there are more cases of chronic rheumatism today than of heart disease, tuberculosis and cancer combined.'

" The prospect of bringing under control a scourge inflicting so much human misery and so much economic wastage must appeal to all, and the prospect is, I am glad to say, a hopeful one. When we recall the triumphs achieved in recent years by medical research in other fields, we have good cause to believe that this problem of Rheumatic Disease will be solved by persevering effort.

" I hope that before this meeting is over you will agree with me that the Empire Rheumatism Council is capable of undertaking this effort with energy and with skill. Its prospectus—if I may use a term familiar to the City—is before you. In the first place, the list of its Board of Directors should inspire every confidence. It is to a remarkable degree representative of the medical and scientific strength of the nation, supported by many of the political and industrial leaders of the community, whom we may hope to see reinforced as the gravity and urgency of the task is more clearly appreciated. Their aid is important. It is for the scientists to lead us in the discovery of facts; then for the statesmen and the business men to guide us in the practical and economical use of those facts, so that good administration may bring prompt and efficient remedy.

" In the second place, the plan of campaign outlined seems sound. It follows closely the recommendations recently made by our National Health Authority as the result of its investigations into the widespread incidence of the Rheumatic Diseases, and of the measures which give the best hope of relief. You will note the provisions for inter-imperial and international co-operation, and the wise decision that knowledge should be sought from all honest and reasonable sources.

" With a first-class Board of Directors and a good plan of campaign, the Council can also claim to its credit, and as a reason for your support, a fine record of preliminary development work. It does not come before you with merely a scheme, but with evidence that the scheme is already in practical operation. Laboratories have been established with whole-time staffs; special tasks of research arranged in some of the medical schools; skilled inquirers sent to Europe and America to study at first-hand foreign methods of investigation and treatment; and several new treatment centres instituted in Great Britain. Surveying the position today compared with that three years ago, when the Empire Rheumatism Council entered upon its work, it can be described as distinctly hopeful.

"Now we are asked to carry a good beginning on to a happy ending; to make success possible by providing the modest budget estimates for the next few years. I sincerely hope that the request will not be in vain, though I realise today we shall have to be thinking about another Budget—unfortunately, not likely to be a modest one. But we in this country have never allowed a necessary and urgent task of this kind to be neglected because of difficult times.

"So with all confidence I commend to your goodwill the work of the Empire Rheumatism Council."

Lord Horder on the Gravity of the Problem

Lord Horder said: "None of us can have failed to notice the impressive evidences of the recruiting campaign for the Territorials as we arrived at the Mansion House—a campaign in which you, my Lord Mayor, take a regimental as well as a patriotic interest. We are here today to recruit for a most relentless war—a war of attrition, which has been sapping our man-power for generations. It is a war against that powerful and elusive enemy, Rheumatic Disease.

"If we 'let up' in this merciless struggle we expose, as it were, the flank of our nation both in peace and in war; and even at this grave and critical time in our history I am confident that a sustained effort to bring under control this unseen aggressor against our people's health and happiness and our national efficiency will not be judged inopportune, and certainly will not go by default. I say this, knowing that Your Royal Highness has also expressed your belief that, despite other heavy and pressing cares and demands upon us, we should never for one moment relax our efforts here.

"It is a belief that we very much appreciate, as also do we particularly appreciate the personal—not merely the official—interest in this campaign that is not the least part of the support Your Royal Highness gives us.

"I hardly need stress the seriousness of the situation. The Rheumatic Diseases (considering the numbers affected and the disabilities inflicted) are probably the most serious foes of our national health and efficiency. I was forcibly impressed by this fact in my earliest medical days as a worker on the staff of our great City Hospital of St. Bartholomew's. Since then I have become convinced that only a resolute and co-ordinated effort can solve the problems presented by attacks from this disease menacing us, as they do, on so wide a front.

"The Empire Rheumatism Council has undertaken this resolute and co-ordinated effort; and, very briefly, here is our plan of campaign and the progress we have already made:

"*Search for exact and definite knowledge of causes* is our first objective. We must know the causes in order to control with certainty, and to prevent. Visitations of bubonic plague, such as came to this City and to all Europe in earlier centuries, were regarded hopelessly as dread and mysterious calamities until medical research discovered their cause in a disease communicated to man by the parasites of the rat. The ravages of tuberculosis could not be checked, as they are now happily being checked, until the responsible bacillus was identified. The actual causes of Rheumatic Disease are still obscure. We must clear away that obscurity.

"Pursuing this task, we have already at work a small group of permanent research workers; a larger group of part-time workers, assisted by grants; and a very much larger group of honorary consultants, including almost all the scientific members of the Council. You will recognise among their names many who have achieved high distinction in the field of research. To these, with the help they will gain by keeping in touch with fellow-workers in foreign countries, we look for discoveries in due course.

"We must recognise, however, that the enemies which they have to track to their lairs are cunning and skilled in all the arts of camouflage. The research side of our campaign will thus call for patient perseverance. But I venture to say with confidence that there are already some hopeful indications of success. And this I can state with certainty: that our detective staff is keen to follow up promptly every clue. For example, some three months ago, what seemed a hopeful test came to us from a Warsaw University; *within a week full particulars of it were in our hands, within a month* scientists were at work in three British centres to evaluate it.

"Another research objective, pursued concurrently, is to study all methods of treatment now practised at home and abroad, and all reasonable suggestions for new methods of treatment.

"Last year two Travelling Research Fellows were sent to Europe and America on tours of direct investigation. As you will probably recognise, printed reports and correspondence cannot always give a completely true picture of a method of treatment. To see the practitioner at his work in the hospital ward or the laboratory gives a clearer impression. The observations of these Travelling Fellows are just now to hand. Judging by a cursory examination of them, they will prove of considerable service.

"Much other research into the means of treatment is being carried out in hospitals and clinics in the United Kingdom. Part of this is intended to arrive at what I might call a more precise evaluation of methods which are in common practice, in order that the most promising can be sifted from the rest. Another side of the work is

directed to the investigation (clinically and in the laboratory) of suggested new methods which give promise of usefulness.

"I must direct your attention here to a grave deficiency which faces us. The means for applying treatments in Great Britain are sadly lacking; we must—somehow and soon—correct this lack, because it is quite evident that, even though the incompleteness of our knowledge of the causes of the diseases handicaps progress, we already have to our hands for immediate use systems of treatment which, if applied in the early stages and patiently pursued, will save the majority of sufferers from the curse of needless pain and subsequent crippling disability.

"As yet these means are available to far too small a percentage of patients. To make them available to all is an aim that we must stress, and we are making some progress towards this. The number of our Treatment Centres has increased perceptibly—I use this word deliberately, because unfortunately I cannot yet use any stronger one; but it *has* increased perceptibly since the foundation of this Council. In some cases, such as the excellent new Rheumatism Departments of the Hospital of St. John and St. Elizabeth, and of the West London Hospital, these clinics have been founded in close co-operation with our Council. In other cases they have come into being following the growing tide of attention aroused mainly *by* our Council on this menace of rheumatism.

"And here I would like to say how sincerely grateful we are to you, gentlemen of the Fourth Estate, for your help in this matter of educating the public as to the real seriousness of this disease.

"Apart from the appeal of human pity—an appeal that in these brutal times we cannot too strongly and too often stress in respect of our own as well as other peoples—the practical aspect, the question of human wastage arises. We must not let our men, women or children drift into incurable disability when they can be saved. And that is why I would stress our hope, which I know is shared by Your Royal Highness, that very soon we shall be able to report not merely a 'perceptible,' but a striking increase in the number of Treatment Centres of all types.

"It is fitting that at this point I should most gratefully acknowledge the splendid degree of assistance we have received, and are receiving, from various public bodies. The Ministry of Health has been cordially helpful from the very outset, and I would like to read from a letter I have received from the Minister of Health, the Right Honourable Walter Elliot, which concludes:

"'The real danger of these diseases tends to be overlooked by the common man, and it is the more necessary that they should be studied closely by the expert. Research both into the causes of Rheumatic

Disease and into methods of treatment is the primary requirement at the present time. In promoting such research, the Empire Rheumatism Council is fulfilling its most important function, and in this, as in its other activities, I wish it every success.'

"Again, the Admiralty, manning so important a rampart of the Empire's security, has paid us the honour of asking our assistance to cope with the incidence of Rheumatic Disease in the training establishments of the Royal Navy, and in co-operation with the Naval Medical Services we have set up an important Research Foundation. The Foreign Office, too, has given valuable help to our research investigations abroad. The London County Council Medical Services, which have to their credit probably the best plan in the world for checking juvenile rheumatism, have been most helpful; also the British Red Cross Society and several of the great hospitals.

"Not last, nor least, are we indebted to you, my Lord Mayor, for summoning this Mansion House meeting. When the City of London speaks, there speaks democracy in action, a free people freely settling its own affairs, and this fact is not overlooked by our own folk nor by those peoples who have not the privilege of belonging to the peaceful Commonwealth of Nations that is our British Empire. And the City does not speak without due cause. This War on Rheumatism, this offensive and defensive war against the too-long-tolerated aggression of this miserable disease, must not degenerate into a trench warfare of unambitious attrition with its draining of human life. We want National Service against Rheumatism . . . if only for the lowest motive, that all are liable to the menace.

"Therefore, my Lord Mayor, Your Royal Highness, my Lords, Ladies and Gentlemen, I propose the following resolution:

> "THAT this meeting recognises the urgent necessity of a National Campaign of research into the causes and best methods of treatment of the Rheumatic Diseases; affirms its confidence in the plans of the Empire Rheumatism Council; and urges the community to support the Council with the means to carry its aims to success."

The Earnest Work of the Council

Sir William Willcox in seconding the resolution said: "It is my privilege to second the resolution which has been proposed by my friend and colleague, Lord Horder, and to undertake the somewhat difficult task of adding to the most effective and admirable statements of our case already made by you, my Lord Mayor, by Your Royal Highness, and by Lord Horder.

"One point I should like to emphasise is that our Council, in its constitution and its working, is a truly Imperial body. We of the

Mother Country recognised from the outset that our peoples overseas, owing allegiance to His Gracious Majesty the King, would wish to share in the great task we have undertaken for the relief of humanity from the grievous scourge of Rheumatic Disease. We have already an affiliated Council established in Canada; another in course of formation in Australia; we expect soon that New Zealand and South Africa will add their strength to the campaign. Also, we have had active support from many of the Crown Colonies; from the remote Falkland Islands, the most southerly outpost of the Empire; from Sierra Leone, a colony which is a monument of another great campaign of human welfare, the Abolition of the Slave Trade; from Hong Kong in the Far East; from Fiji, and from other lands under our flag. Some of these have less direct interest in Rheumatic Disease, being not so much exposed to its attacks, owing to their climate and living conditions. They recognise, however, this as a good work for the security of the Empire which shelters them, and probably also are sensible of the great blessings which have come to them from other medical research campaigns. We aim to recruit all the forces of the British Empire to co-operate with us in our campaign against Rheumatic Disease.

"As Chairman of two key Committees of the Council I should like to testify to the devoted and energetic work carried out by the members of all Committees. A spirit of zeal and a sense of urgency characterise their work, which takes first place in spite of many other claims on their time. The Executive Committee has the benefit of the wise counsel of lay members of great experience in the world of affairs, and in its financial undertakings has the great advantage of the sound advice of the Finance Committee, of which Mr. T. W. Robinson is Chairman. The Research Advisory Committee, which is composed entirely of medical men, and on which the Medical Research Council is represented, gives wise guidance in the schemes of research undertaken, and recommends the extent of financial support of which these are worthy. It also gives guidance and advice to the research workers of the Empire Rheumatism Council and receives periodic progress reports of their work. The Scientific Advisory Committee, under the able chairmanship of Dr. H. Mervyn Gordon, makes preliminary investigations into proposed schemes of research before these are placed before the Research Advisory Committee. It is doing valuable work in the testing of suggested new remedies for rheumatism and determining their efficacy. It is also aiming at the standardisation and valuation of methods of treatment in general use.

"I should like to call attention to the valuable support given to the research in Acute Rheumatism by the Sir Halley Stewart Trust, and also to the splendid help given to this special research work by

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"I should like to call attention to the valuable support given to the research in Acute Rheumatism by the Sir Halley Stewart Trust, and also to the splendid help given to this special research work by

a generous American citizen, Mr. Frederick Pearson, who has contributed over £4,000.

"Modern research has demonstrated the close association between Rheumatic Fever and the various forms of Chronic Rheumatism. Our Council feel that a solution of the ætiological problem of Acute Rheumatism will be of great help in the determination of the cause of Chronic Rheumatic Disease.

"I am pleased to say that encouraging results have already been achieved. I express also my appreciation of the valuable work carried on by the Treatment and Hospitals Committee under the able chairmanship of Professor L. S. P. Davidson, who has done so much to help the work of the campaign in Scotland.

"I can convey a message of hope and optimism regarding our work. Arthritis and Chronic Rheumatic Disease were formerly regarded as incurable. The modern methods of treatment have been attended with increasing success and an encouraging percentage of cures has already been attained. One of the most important factors for success is early treatment. At the commencement of the illness causal factors can be ascertained and often eradicated, when a permanent cure naturally follows."

After expressing his thanks to the Organising Secretary, Sir Frank Fox, and the staff for their work, Sir William Willcox continued:

"Let me ask your attention for a moment to the practical issue: the need for the munitions of war. In making our plans we estimated that a sum of half a million pounds from the Home Country and from the Overseas Empire would be sufficient, with careful economy of administration, for the seven years' term of our campaign. We assigned to London and the Home Counties, as their share of the effort, £150,000. That, I think, is an insignificant sum in view of the fact that, apart from its tragic toll of human suffering, Rheumatic Disease is costing our community some scores of millions of pounds annually in loss of working time. Of that £150,000, we have secured by private subscriptions to date just over one-third, in round figures £51,000. We look forward to the balance coming to hand promptly.

"In this regard I wish to acknowledge with sincere gratitude the help given to Treatment Centres associated with our Council by the City of Westminster, the Royal Borough of Kensington, and the Boroughs of Fulham, Hammersmith and St. Marylebone. To them I express thanks for their wise and public-spirited action.

"I beg to second the resolution. It affirms your confidence in the Empire Rheumatism Council. I trust that the general public will share that confidence, and that we shall justify it to the full."

The resolution was carried with acclamation.

Sir Joseph Burn proposed: "That a hearty vote of thanks be

accorded to H.R.H. the Duke of Gloucester for his gracious presence today, with the earnest hope that under his Presidency the Empire Rheumatism Council will succeed in its great task."

Sir Joseph Burn said: "It was the recent comment of a distinguished American observer that the British Empire is fortunate in having in its Royal Family 'the finest team of first-class workers in the world.' That was a true observation. Many of us are often moved to wonder how it is possible for our Royal Princes—and not forgetting our Royal Princesses—to find the time and the energy to enter so fully into all the social and philanthropic activities of the community.

"The importance of the task of the Empire Rheumatism Council cannot be exaggerated. Rheumatic Disease is probably in our country the greatest foe to human happiness. It is responsible every year for spoiling the lives of thousands of young people, bringing them either to premature death or to loss of all prospect of useful life; and on adults it inflicts such suffering that in very many cases death is looked upon as a happy release.

"The speeches which we have heard today and the records of the work already undertaken by the Empire Rheumatism Council convince me that in that Council we have the right body of men to deal with the great curse of rheumatism and that they are working on the right scientific lines.

"When I tell you that the Prudential Approved Societies spent during 1938 nearly £3,500,000 on sickness and disablement benefit you will realise that the amount paid by these societies in respect of rheumatism must be a very large sum."

Mr. A. G. Timbrell Fisher, in seconding the resolution, cordially and confidently endorsed the hope with which it concluded. This serious scourge of Rheumatic Disease called for every effort that was humanly possible to bring under control its ravages. As to their extent in our community, a significant fact had been brought to his notice by Sir Benjamin Cohen: that in his task of administering Old Age and Widows' Pensions three out of four of the applicants, men and women, were crippled with Rheumatic Disease.

The Council were deeply indebted to His Royal Highness for accepting its leadership. It was of good augury for success.

The resolution was carried with acclamation.

Mr. J. Spedan Lewis (who was the first financial supporter of the Empire Rheumatism Council, contributing personally £1,000, and in addition collecting among his friends an almost equal sum) proposed the final resolution: "That a hearty vote of thanks be accorded to the Rt. Hon. the Lord Mayor of London, Major Sir Frank Bowater, for presiding at this meeting."

Sir Walter Kinnear, in seconding the resolution, said that of the many deserving objects which the Lord Mayor had supported during his term of office, there was not one which surpassed in urgency and importance the work of the Empire Rheumatism Council. The Rheumatic Disease group knew no frontiers, was no respecter of persons, claimed youth and age alike as its victims. . . . The pity of it was that much of all this was preventable. The available evidence suggested that Rheumatic Disease could and would be conquered. The eminent medical men and scientists who were giving their services so freely and ungrudgingly to the work of the Council were satisfied that an intensive study into the chief causative factors of rheumatism, concurrently with a methodical research into the most efficacious methods of treatment, could not fail to result in a marked reduction in the incidence of this hitherto baffling disease.

He hoped, under the inspiring leadership of His Royal Highness and the Lord Mayor, there would be a quick and generous response from every section of the public, so that the Council could carry on its work on a wide and intensive scale, free from financial anxiety. Parliament had work of that kind in mind when it expressly permitted by legislation the National Health Approved Societies to make donations out of their surplus money to medical research.

The resolution was carried with acclamation.

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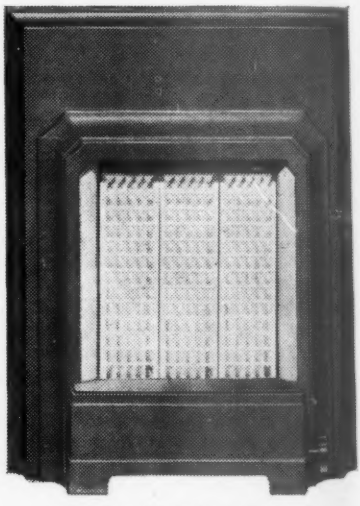

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